Usefulness of home spirometry in childhood asthma

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Stellingen behorende bij het proefschrift
'Usefulness of home spirometry in childhood asthma'

1 The unreliability of written PEF diaries can be overcome by using home spirometry. *(this thesis)*

2 The variable concordance of PEF variation to other parameters of asthma severity limits the usefulness of home spirometry for monitoring disease severity in childhood asthma. *(this thesis)*

3 The variable concordance of changes in PEF variation to changes in symptom scores in children with asthma makes it unclear to patients in asthma self-management, how they should respond to what change in which parameter. (*this thesis)*

4 The reliable single reference value of lung function variation for schoolchildren, obtained by home spirometry, is substantially lower than the one previously described using a traditional peak flow meter and a written diary. *(this thesis)*

5 The marginal contribution of lung function variation to make the diagnosis of asthma limits the usefulness of home spirometry as a diagnostic tool for childhood asthma in children with nonspecific cough or breathlessness. *(this thesis)*

6 The theoretical benefit of the ability of home spirometry to measure FEV_1 in addition to PEF did not bear out in practice. *(this thesis)*

7 Based on the limited usefulness of home spirometry, and the proven superiority of monitoring symptoms over lung function variation, international guidelines should discourage the use of lung function monitoring both for diagnosing and following up asthma in children. *(this thesis)*

8 The way we communicate with others and with ourselves ultimately determines the quality of our lives. *(Anthony Robbins)*

9 Any fool can make things bigger, more complex, and more violent. It takes a touch of genius - and a lot of courage - to move in the opposite direction. *(Albert Einstein)*

10 Het zorgen voor (eigen) kinderen in de privésfeer blijkt een van de meest leerzame stages in de opleiding tot kinderarts.

11 Happiness is not something ready made. It comes from your own actions. *(Dalai Lama)*

Alwin Foppe Jan Brouwer, Groningen, 20 januari 2010

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Chapter 1

Introduction

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Introduction

Asthma is the most common chronic disease of childhood, with millions of children affected worldwide.[1] Over the past decade, guidelines for the diagnosis and treatment of asthma, such as the Global Initiative on Asthma (GINA) guidelines, have increasingly adopted an evidence-based approach for retrieving and analysing published studies.[2]

These evidence-based asthma guidelines divide the principles of care in childhood asthma into a number of key steps.

Diagnosis. The first step, obviously, is to make the diagnosis of asthma. Asthma in children, and adults, is a clinical diagnosis.[2] There is no gold standard test for asthma. The main diagnostic tool for asthma is the history, with symptoms such as episodic breathlessness, wheezing, cough, and chest tightness. Because patients and parents vary considerably in their interpretation of "wheeze" (which may include any kind of noisy or difficult breathing),[3,4] the presence of expiratory wheeze, as a sign for the presence of airflow obstruction, should be confirmed by a health care professional, either by physical examination or by lung function testing.[2,4,5] Hospital based spirometry can be used to confirm the diagnosis. However, due to the variation of airway obstruction, a key feature of asthma, these snap-shot lung function tests lack sensitivity.[2] Repeated daily home measurements of peak expiratory flow (PEF) have therefore been advocated to document the variation of lung function, both for making the diagnosis,[6] and for monitoring the response to

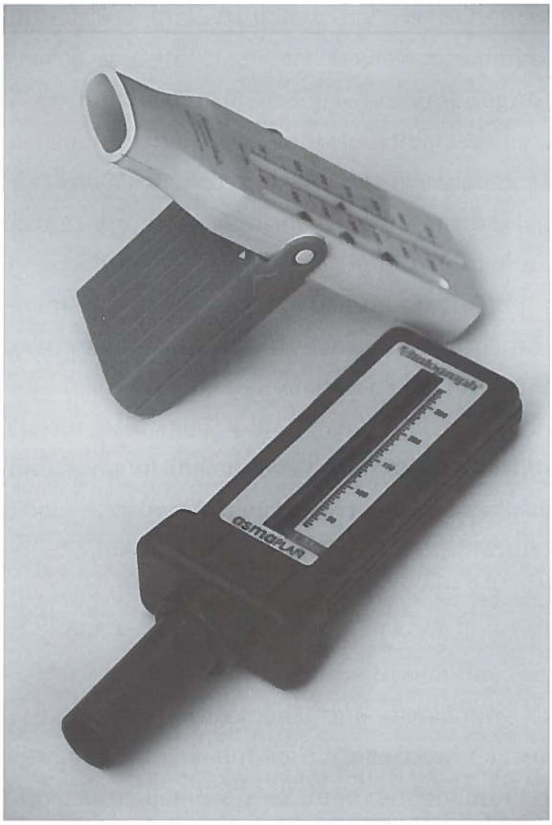

Figure 1. Mechanical peak flow meters. Peak flow meters use a sliding marker which moves during forced expiration along a numbered scale. The results are recorded by patients in an accompanied written peak flow diary.

asthma treatment.[2,7] Originally, such home monitoring of PEF was performed on simple, cheap, mechanical PEF meters (figure 1), and measurements were recorded in a written diary.

These written PEF diaries, however, proved to be very unreliable, with as much as 50% of values in the diary either being invented or recorded incorrectly.[8] As a consequence, results from earlier studies using written PEF diaries to measure variation of lung function should be questioned and reassessed.[9] The use of electronic home spirometers (figure 2) has been advocated as a suitable alternative to mechanical PEF meters to establish the variation of lung function. These devices store the recorded lung function values electronically on a microchip, and are

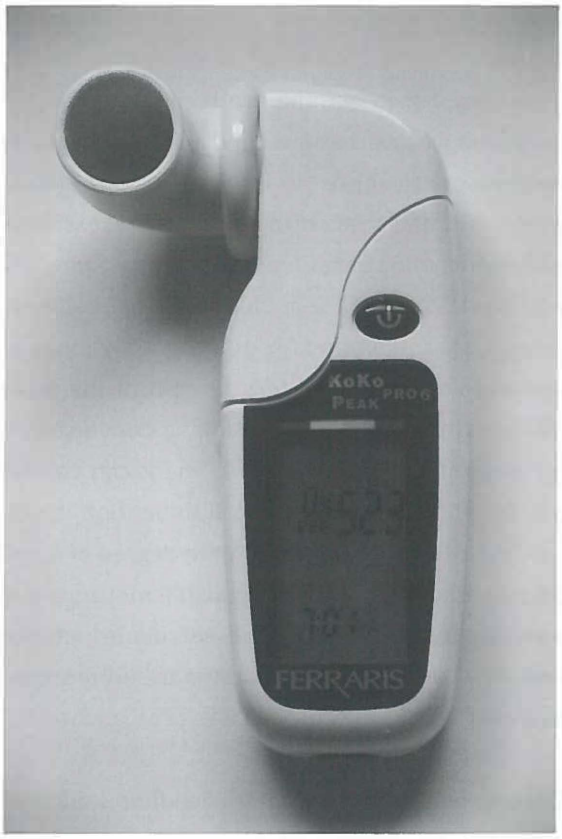

Figure 2. Koko Peak Pro. Electronic hand held home spirometer, measuring peak flow, FEV_1 and FVC. The results are saved in an incorporated microchip and can be downloaded on a computer.

supposed to be much more reliable than written PEF diaries.[2,7,8] The value of home spirometry in the diagnosis of asthma has never been formally studied, however.

Identification of triggers, and reduction of exposure to relevant triggers. A second important element of childhood asthma care is the identification of stimuli that induce symptoms ("triggers") and reduction of exposure to these triggers. Exacerbations of asthma can be triggered by a number of stimuli, including viral respiratory tract infections, exercise, exposure to allergens, or exposure to pollutants such as cigarette smoke and traffic exhaust particles.[10-12] When possible,

reducing exposure to these triggers may improve asthma control and reduce medication needs.[2,7,12]

Pharmacotherapy. Although asthma is not curable, pharmacologic interventions to treat established asthma are highly effective in controlling symptoms, reducing or preventing exacerbations, and improving quality of life, lung function, and airway hyperresponsiveness.[13,14] Inhaled corticosteroids (ICS) are the cornerstone of asthma treatment, and these drugs should be prescribed on a daily basis to all children with persistent symptoms (complaints on more than two days per week).[2,7,13,14] In addition to these daily preventive drugs, each patient should be provided with short-acting bronchodilators for quick relief of symptoms on an as needed basis.[2,7] If this approach to treatment fails to control the disease satisfactorily, drug treatment is increased in a stepwise fashion.[2,7] Conversely, when asthma control is maintained for at least three months, treatment can be stepped down in reverse order. [2,7] The outcome of pharmacologic intervention studies almost invariably includes the number of exacerbations and the degree of lung function variation over time. This is usually assessed by mechanical PEF meters and written PEF diaries.[15] Because of the unreliability of these written PEF diaries, studies using home spirometry to assess and monitor treatment response are preferable. Very few such studies are available, however.

Education. A key element in childhood asthma care is education of patients and parents. This includes an explanation of the different aspects of the disease and its treatment, and teaching the management skills needed to achieve optimal asthma control. Educating asthmatic children and their parents is a complex intervention, and it is difficult to assess which components of education are particularly useful. A prerequisite for education and self-management of paediatric asthma is the development of a partnership between the asthma patient, his or her parents, and the health care professionals.[2] Building such a partnership requires good communication skills by the health care providers.[16] The main aim of the partnership is to provide patients with asthma the knowledge, confidence and skills to control their own condition, with guidance from health care professionals, and ultimately to establish a degree of independence.[17] This requires a comprehensive education package, delivered in repeated sessions over prolonged periods of time.

One of the key elements in asthma education is teaching the patient how to respond to deterioration of the disease. This requires a certain degree of monitoring of disease activity, and this is the final main element of childhood asthma care.

Monitoring of disease activity. Asthma guidelines recommend two approaches to objective monitoring of disease activity. Office-based assessment of lung function is usually performed by obtaining full expiratory flow-volume curves to assess airway obstruction. If obstruction is present, its reversibility can be tested by repeating flow-volume curves after inhaling a bronchodilator. The degree of airway hyperresponsiveness assessed by bronchial challenge tests is not routinely recommended.[2] Although there are no RCTs demonstrating the usefulness of annual office spirometry in the follow-up of childhood asthma,[18] ample observational evidence supports its use.[19,20] Inflammatory markers such as fractional exhaled nitric oxide (FeNO) are still being evaluated for potential use in monitoring disease activity, but are increasingly used in clinical practice.[2] Although evidence to support the use of home monitoring of PEF is lacking,[9,18,21,22] and accumulating evidence suggests that it does not contribute to optimizing asthma control,[21-23] asthma guidelines still advocate the use of home PEF monitoring.[2,7] Most studies on home PEF monitoring used written PEF diaries. There is a need, therefore, for additional studies on electronic home spirometry as a monitoring tool in childhood asthma.

Because education is a key issue in successful asthma management, the following section of this introduction will summarize and discuss the results of systematic reviews on education in childhood asthma. As the majority of educational interventions in asthma also include monitoring of disease activity, the different approaches to asthma monitoring in children will be discussed. This leads to the presentation of the individual studies on home spirometry in this thesis.

Systematic reviews of education in asthma

It is not clear whether randomized controlled trials and meta-analyses of results of such studies in systematic reviews are valid and useful to study complex interventions where a comprehensive set of medical deliberations, technical skills and local circumstances, which are all difficult to standardize, may influence the outcomes studied.[24] Because the education of asthmatic children and their parents is such a complex intervention, evaluating the effects of this intervention with evidence-based medicine techniques is fraught with difficulties. It should come as no surprise, therefore, that systematic reviews of education in childhood asthma have come to divergent conclusions,[25,26] and that many studies have been eliminated from systematic reviews because of insufficient methodological quality or clinical heterogeneity.[23,25,27,28]

The Cochrane Library contains four systematic reviews on educational strategies in childhood asthma.

Educating children who have attended the emergency room for asthma.[27]
This review included eight studies involving 1407 subjects. Compared to controls, education did not reduce subsequent emergency department visits (relative risk 0.87, 95% confidence interval 0.37–2.08) or other healthcare use variables. Clinical heterogeneity was a major problem, both within and between studies. Perhaps the most striking finding of this review was that most studies showed modest beneficial effects (figure 3),[29,30] but this was offset by a single large trial showing the opposite effects.[31]

This latter study was conducted in New Zealand in the early 1980s. Usual care was compared to education which consisted of monthly home visits by asthma nurses. The subjects were assessed 6 months later by a postal, self administered questionnaire. European children in the education group were more likely to return to hospital for severe attacks than those in the control group, but such differences were not seen in Polynesian children. The main limitation of this study is that fewer than one-third of children used inhaled corticosteroids.[31] Although this study had a major impact on the results of the systematic review,

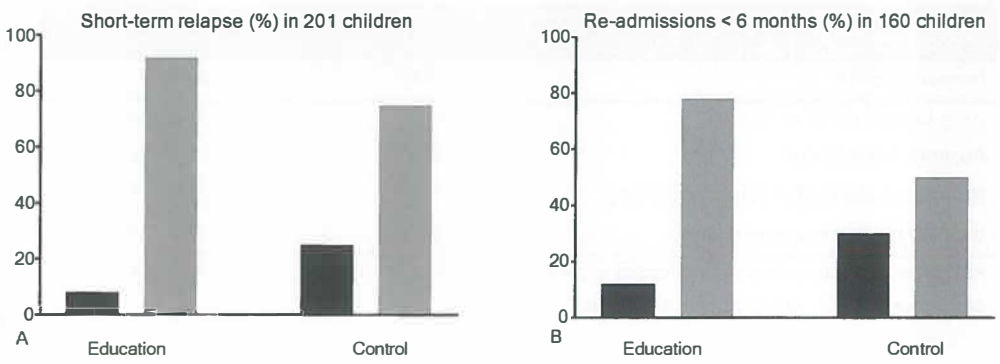

Figure 3. Effect of education on short-term and long-term asthma relapse rates in children admitted to hospital for acute severe asthma.[29,30] Black bars represent A) relapse or B) re-admissions; gray bars represent A) no relapse or B) no re-admissions.

the treatment of the children involved is no longer representative of current practice, and the results can, therefore, not be extrapolated to today's children with asthma.

Educational interventions for asthma in children[32]

This review evaluated the effects of education in children with chronic persistent asthma. This review, which was also published as a journal article,[28] included 32 studies involving 3706 patients. Asthma education programmes were associated with moderate improvements in a number of clinically relevant asthma outcome measures (table 1).[32]

Although this meta-analysis provided strong support for the usefulness of education as a general approach, it also suffered from clinical heterogeneity. In particular, it was noted that there were many different educational approaches and that direct comparisons between these different educational programmes were lacking. Thus, it was impossible for the reviewers to judge which educational approach was most effective. The only comment made was that the effects of peak flow-based education and monitoring programmes seemed to be larger than those based on education alone.[28]

Table 1. Beneficial effects of educational interventions in children with chronic persistent asthma (systematic review of randomized trials comparing education to regular care without education).[28,32]

Improvement in	SMD	95% CI
Lung function (PEF or FEV_1)	0.50	0.25 to 0.75
Absence from school	0.14	0.04 to 0.23
Number of days with restricted activity	0.29	0.09 to 0.33
Visits to emergency department	0.21	0.09 to 0.33

PEF: peak expiratory flow; FEV_1: forced expiratory volume in one second; SMD: standardized mean difference; 95% CI: 95% confidence interval.

Written action plans for asthma in children and adults[25]

This systematic review examined whether a written asthma self-management plan improved outcome (as compared to no written action plan). This review, published in 2004, comprised seven studies and 967 patients (primarily adults; one study involved 46 children), and showed no consistent effect of a written action plan on any asthma outcome.[25] The main drawback of this analysis from a paediatric point of view was that only one study included children and that these children were not analysed separately from the adults. In addition, large differences between the different educational programmes were again noted.

Another systematic review, published as a journal article in the same year but not included in the Cochrane database, also explored the usefulness of written action plans in asthma management. This review included 26 trials, and found that individualized written action plans based on personal best peak flow, using two to four action points and recommending both inhaled and oral corticosteroids for treatment of exacerbations, consistently improved asthma health outcomes.[26] In this meta-analysis, no differences were found between peak flow and symptom-based plans.

At face value, it is quite striking that two systematic reviews with the same aim and similar methodology include a highly different number of studies, and come to completely opposite conclusions. As discussed above, however, this is an illustration

of the problems involved in analysing results of complex interventions with methods developed for another purpose (namely, to evaluate drug therapy).

Written action plans for asthma in children[23]

The most recent Cochrane review analysed the results of studies on the effects of written asthma plans in children. This analysis comprised four trials involving 355 children. Children following a symptom-based written action plan had a 27% lower risk of exacerbation requiring acute medical care than children on a peak flow-based action plan (relative risk 0.73, 95% CI 0.55–0.99); the number needed to treat was 9 (95% CI 5–138). Conversely, children assigned to a peak flow-based education plan had slightly fewer symptomatic days per week than children assigned to a symptom-based action plan (mean difference 0.45 days; 95% CI 0.04–0.86 days).[23] The review was unable to answer the question whether written action plans per se improved asthma outcomes because no studies compared a written action plan versus regular care. Other weak points in this review were the small number of studies involved, and, again, clinical heterogeneity.[33]

What can be learned from systematic reviews on education in childhood asthma?

It is clear from the discussion above that very few firm conclusions can be drawn on the effects of education in children with asthma. There is little doubt that education in itself is useful (table 1).[28,32] This is, of course, both not very surprising and not very helpful to practice – no paediatrician in his or her right mind would try to treat a chronic condition in a child without at least some basic explanation to the child and parents on the nature of the disorder and the logic of its treatment. The challenge, therefore, is not to justify education per se, but to try and tease out which components of education are useful and which are well-intended but superfluous. Unfortunately, the systematic reviews performed to date do very little to address this challenge. For example, even though written action plans have been promulgated as the standard of care over the last 20 years in children with asthma, no study has evaluated its efficacy in children.[34] This absence of good quality evidence may help to explain why so few patients actually receive a written action plan in practice,[34,35] despite the guidelines' insistence on its importance.[2] This also

illustrates that the evidence base for such recommendations on asthma education in 'evidence-based' guidelines is, at best, shaky. Because it is difficult to study asthma education in randomized controlled trials, additional support for recommendations in guidelines should come from observational studies.

The problem of clinical heterogeneity

So far, all studies on asthma education have lumped together all patients with asthma. All systematic reviews have noted that clinical heterogeneity is a major problem, not only because of the differences between educational programmes, but also because of differences between asthma patients. Any given educational approach may be useful in some children with asthma but not in others. What is useful for school-aged children may not work in toddlers.[36] What is valid for chronic persistent asthma may not be valid for children hospitalized for asthma. Even within studies on acute severe asthma in children, clinical heterogeneity appears to be a major problem:[37] not every asthma exacerbation appears to be the same. Although an exacerbation of asthma can occur against the background of poor asthma control,[33] it has also been shown that children with well controlled asthma may show isolated, sometimes quite severe, exacerbations associated with viral infections, and this may be viewed as a distinct asthma phenotype in childhood.[38] The importance of different asthma phenotypes is being increasingly recognized across all ages.[39] Clearly, in future studies on any therapeutic intervention in childhood asthma, a clear and detailed description of the patient population studied is needed. Only then can we begin to understand in what way and to what extent different asthma phenotypes in childhood respond differently to educational interventions.

Education: what should be explained to parents and children?

No studies have evaluated which components of asthma education determine its success. Virtually all studies have examined a comprehensive package of educational and monitoring strategies (table 2) and, because this is the only approach that has been extensively studied, guidelines tend to recommend application of the entire programme.[2] Although this may be regarded as the safest approach (the effects of this package have been demonstrated), it is not necessarily the most effective one.

In particular, there is good evidence against home monitoring of lung function, as will be discussed below.

As outlined above, it is only logical that children with a chronic condition such as asthma and their parents should receive information on the causal mechanisms of the disorder. Remarkably little is known, however, on the content of this information or how it should be presented to patients and their parents. A recent study showed that most adult patients with asthma preferred an active or at least collaborative role in the management of their disorder, but that most perceived their role as passive.[40] Similar results have been found in parents of children with eczema,[41] but to our knowledge this has never been studied in children with asthma. There is some evidence that family interaction and dynamics may play a role in how parents view their child's disease and how likely they are to follow educational advice.[42,43] A questionnaire has been developed to assess these 'family asthma management routines',[44] but the usefulness of this questionnaire has not been fully elucidated.

Numerous asthma education packs are available online (e.g. at www.ginasthma.org). Most centres will adapt these to their own needs and circumstances. For example, based on the evidence available to date and our own experience in providing asthma education to hundreds of patients, we have put together an extensive information package for children with asthma and their parents. After the diagnosis has been

Table 2. Components of a typical asthma education package

Education and training	1	Explanation of the causal mechanisms of the disorder, trigger factors and pattern of symptoms
	2	Explanation of difference between maintenance treatment and symptomatic treatment
	3	Instruction and practice of correct inhalation technique
Supportive treatment	4	Explanation of deleterious effects of tobacco smoke exposure, and support to prevent exposure of child to tobacco smoke
	5	Discussion of role of allergen exposure, and support to avoid it
Monitoring	6	Home monitoring of symptoms or peak flow
	7	Instruction on self-management: what to do when asthma deteriorates (for example, written action plan)

made and a treatment plan has been outlined, the attending paediatrician discusses the salient information items with the patient and parents. This is then reinforced by repeated education sessions with one of our asthma nurses,[45] by the written information package and by a list of reliable online information sources (including our national Asthma Foundation). We aim for regular and long-lasting follow-up visits if necessary, and at every follow-up visit, the importance of maintenance treatment is stressed, and questions and concerns are addressed.

Instruction on correct inhalation technique

Inhaled asthma treatment can only be expected to be effective if the inhaler is used properly. In accordance with others,[46,47] we found that many children with asthma use their inhaler incorrectly.[48] To our surprise, however, this was not only due to lack of proper instruction; poor inhalation technique was also common in children who had received inhalation instruction in primary care.[48] This prompted us to study the determinants of correct inhalation technique in children in more detail.[49] Two hundred children attending our asthma clinic for a scheduled follow-up visit were interviewed about the inhalation instruction they had received in the past, and subsequently demonstrated the use of their own inhaler. Inhalation technique was scored using a validated scoring system identifying steps considered to be essential for reliable drug delivery.[48,49] Even though 99% of patients had received inhalation instruction and 96% of patients were confident that they could use their inhaler correctly, 92/200 children tested (46%) used their inhaler incorrectly. Correct inhaler use was not dependent on age, sex, type of inhaler, or duration or severity of asthma. Two features of inhalation instruction, however, were significantly associated with correct inhaler technique (table 3).

Table 3. Determinants of correct inhalation technique in 200 children with asthma, attending a secondary care asthma clinic (adapted from[49]).

Characteristic	% present in children with correct inhalation technique	% present in children with incorrect inhalation technique
Instructor demonstrated correct technique	78%	80%
Video instruction	26%	26%
Patient demonstrated technique	64%	45% (p=0.03)
Instruction repeated	65%	23% (p<0.001)

Patients (or parents, depending on the age of the child) who had to demonstrate the use of their inhaler to the asthma nurse during instruction sessions were more likely to maintain a correct technique than patients who were only passively instructed. By far the most important factor, however, was repetition of inhalation instruction (table 3). The odds of a correct inhalation technique increased eightfold when inhalation instruction sessions were repeated (95% CI 3.2–21.5). The usefulness of repeated active demonstration of correct inhalation was then tested prospectively in 47 newly referred patients. Only after three repeated instruction sessions over a 6-month period did >95% of patients use their inhaler correctly.[49] This illustrates that achieving and maintaining a correct inhalation technique is difficult, and requires time and repeated effort.

Two observations from our own clinic support the usefulness of this approach. First, in a randomized trial comparing follow-up by asthma nurse or paediatrician in children with asthma, 74 newly referred patients were enrolled in our asthma management programme, comprising extensive repeated education and repeated inhalation instruction sessions.[45] There were no differences between the two study groups in any of the asthma outcome parameters studied, showing that childhood asthma can be effectively and cost-effectively followed up by asthma nurses.[45,50] All 74 patients referred because of troublesome asthma showed significant and clinically relevant improvements in airway hyperresponsiveness and quality of life after 1-year follow-up at our clinic.[45] This was not due to more intensive medication use. In fact, the mean inhaled steroid dose could be reduced by, on average, 26% (figure 4). The proportion of patients with a correct inhalation technique increased from 65% at baseline to 95% after 1-year follow-up. This clearly illustrates that with extensive education, training in the correct use of the inhaler device and close follow-up, childhood asthma can be well controlled. Second, a cross-sectional analysis of lung function values in 301 children with asthma attending our clinic showed, on average, normal FEV_1 values in these patients. In fact, reduced lung function levels were only observed in patients experiencing an acute episode of asthma, or in those with poor adherence to maintenance medication.[51]

These observations clearly illustrate that with extensive education, training in the correct use of the inhaler device, and close follow-up, childhood asthma can be well controlled and normal lung function maintained.

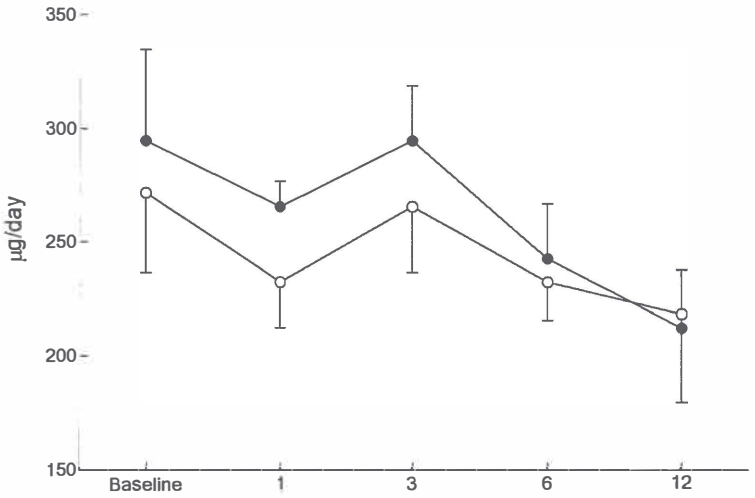

Figure 4. Mean (SE) dose of inhaled corticosteroids (ICS) during the study for patients followed by a paediatrician (○, n=28) or asthma nurse (●, n=30) and who had already been prescribed an ICS by their general practitioner. Reproduced with permission from Kamps et al.[45]

Monitoring: symptoms or peak flow?

An integral component of asthma education and follow-up is monitoring of disease activity. Self-management of asthma in children relies heavily on the ability of patients and parents to gauge the severity of the disorder on a day-to-day basis, and to respond appropriately to imminent deterioration. Home monitoring can be either symptom-based or peak flow-based. Guidelines prefer home monitoring of peak flow, primarily because it is assumed that many children with asthma are 'poor perceivers' of airway obstruction, and because it is assumed that peak flow-based self-management improves asthma outcomes.[2] There is no good evidence to support either assumption, however.

First, poor perception of airway obstruction is more common in children with undiagnosed asthma than in children with diagnosed asthma.[52] In addition, little is known about the variation of accuracy of symptom perception between children

with asthma. Finally, the clinical significance of differences in symptom perception between children in determining and maintaining asthma control is unclear. In a large group of asthmatic children followed up for 1 year, for example, poor perception of dyspnoea was not associated with emergency visits for asthma or poor lung function.[53]

Second, systematic reviews on the relative merits of symptom-based and peak flow-based self-management plans have yielded conflicting results.[23,26,28] As mentioned earlier, the main disadvantage of home peak flow monitoring is that paper diaries are hopelessly unreliable, with as much as half of the data either invented or incorrectly recorded.[8] It is assumed that this can be overcome by the use of electronic home spirometers. Children show high adherence to home spirometry and perform these measurements in a technically correct manner.[54] So far, one randomized trial compared symptom-based self-management to home spirometer-based self-management in 90 children with asthma, and found no differences in asthma outcomes over a 3-month period.[22]

Previous studies using paper PEF diaries have examined the relationship between peak flow or peak flow variation and other indices of asthma severity, and found that monitoring PEF alone is insufficient to assess asthma severity adequately.[55-57] A 20 month longitudinal study in 104 children found poor concordance of changes in PEF variation with changes in other parameters of asthma severity.[56] Another 12 month longitudinal study in 192 children did find an association between lower respiratory tract symptoms and falls in PEF in children.[55] However, in that particular study, half of the exacerbations were preceded by respiratory symptoms 2 days prior to a fall in PEF. Even more surprising, about 40% of the registered PEF episodes were not accompanied by symptomatic events.[55] A diagnostic study in 120 children found a low sensitivity and a high false negative ratio using PEF variation to make the diagnosis of asthma.[57] All these studies recommend PEF monitoring, but only as an additional measurement, and not as an isolated monitoring or diagnostic tool. Due to the unreliability of written PEF diaries,[8] however, it is uncertain whether these earlier results are valid. Therefore, the relationship between asthma severity and peak flow variation should be studied by electronic home spirometry. Despite its proposed usefulness,[2,58] studies on the reliability and clinical application of home spirometry in children are lacking. Only one study examined the validity of electronic home spirometry.[59] It compared its values to those obtained by hospital spirometry,

showing reasonably accurate and reproducible measurements of PEF and FEV_1.[59] The potential benefits of the ability of home spirometry to measure FEV_1 in addition to PEF has yet to be assessed.[53]

Conclusions

Education of children with asthma and their parents is effective in improving clinically relevant outcomes. Common sense dictates that these improvements are most likely to be achieved if the health care team, the child with asthma and his or her parents work together in a partnership.[2] This should include extensive education of the patient and parents on causal mechanisms of asthma, identification of trigger factors and treatment. Adherence to maintenance medication and correct use of the inhaler device are key factors in obtaining asthma control. Achieving and maintaining proper inhalation technique requires time and repeated effort. However, a crucial part of these programmes is probably the level of agreement between the doctor and the patient. Once this has been achieved and a partnership has been established, follow-up can be performed by an asthma nurse. Although home monitoring of lung function is intuitively appealing because it aims at assessing one of the key characteristics of asthma, variation of airway obstruction, its usefulness in the long-term management of asthma is not supported by evidence. Most studies on home monitoring of lung function used mechanical PEF meters and written PEF diaries which are unreliable. Because electronic home spirometers have the advantage of accurately reflecting diurnal and day-to-day changes in lung function, home spirometry may be a useful tool in making the diagnosis of asthma and monitoring the disease.

Scope of this thesis

The main aim of this thesis is to explore the usefulness of measuring lung function variation by electronic home spirometry in the diagnosis and monitoring of childhood asthma. For this purpose, we designed a number of specific studies examining the validity of home spirometry, its usefulness as a monitoring tool, and its diagnostic value.

Validity: In all studies, we used the same electronic portable spirometer (Koko Peak Pro, Ferraris, Louisville, Colorado, USA: figure 2) This home spirometer has been validated *in vitro* using a precision waveform generator (Pulmonary Waveform System; MH Custom Design and Mfg, Midval, UT, USA) demonstrating its agreement with performance standards as recommended by international guidelines.[60] It is fairly cheap, approximately € 40 a piece, easy to use and only needs calibration once during manufacturing. In *chapter 2*, we examined the validity of this home spirometer *in vivo* by studying the agreement between lung function variables measured by home spirometry and those obtained by hospital lung function measurement on a pneumotachograph.

Monitoring: The usefulness of electronic home spirometry to monitor the severity and variation of airway obstruction in asthma after maintenance treatment with ICS has been instituted is described in *chapter 3*. In this study, we assessed the relationships between lung function variation, asthma symptom scores and other indices of asthma severity.

In clinical practice, the dose of ICS is commonly adapted in response to changes in symptoms and need for bronchodilators.[2] Some clinicians even support daily titration of ICS dose in response to daily variation of symptoms and need of rescue therapy.[61] These approaches of variable ICS dosing are based on the assumption that patients are able to recognize airway obstruction reliably. The agreement between symptoms and lung function has been studied in a hospital setting in patients with acute severe asthma.[53,62,63] Both cross-sectional and longitudinal studies have shown poor concordance between lung function and respiratory symptoms,[64-66] but these studies are hampered by the use of unreliable written PEF diaries. In *chapter 4*, we

used home spirometry to study prospectively whether symptoms prompting the use of reliever therapy are accompanied by changes in lung function.

Diagnosis: A population based study using written PEF diaries showed considerable overlap in PEF variation between healthy and asthmatic children,[67] suggesting that measuring diurnal PEF variation was not a useful diagnostic tool for asthma in children.[57] Given the unreliability of written PEF diaries, however, we questioned the validity of this assumption. In *chapter 5*, we describe a study aimed at establishing reliable reference values of lung function variation using electronic home spirometry. *Chapter 6* describes a prospective study to explore the usefulness of lung function variation in diagnosing asthma in children with nonspecific respiratory symptoms.

Chapter 7 provides a summary of the results of the studies in this thesis, and the usefulness of home spirometry in childhood asthma is discussed in a practical clinical context.

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Chapter 2

Comparison between peak expiratory flow and FEV_1 measurements on a home spirometer and on a pneumotachograph in children with asthma

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Abstract

Background

The accuracy of electronic portable home spirometers has been demonstrated in vitro using computer-based waveforms. We assessed the agreement in vivo between measurements of lung function on an electronic spirometer (Koko Peak Pro) and those obtained by the gold standard, a hospital lung function laboratory pneumotachograph.

Methods

Fifty stable asthmatic children (33 boys), aged 6–17 years, performed peak expiratory flow (PEF) and forced expiratory volume in 1 sec (FEV_1) measurements according to international guidelines on a portable home spirometer and on the hospital pneumotachograph in random order. All measurements complied to standard quality criteria. The PEF and FEV_1 values recorded with the home spirometer and on the hospital pneumotachograph were compared.

Results

All children performed reproducible high-quality measurements on both spirometers. PEF values on the home spirometer were considerably lower than on the laboratory pneumotachograph (95% CI for difference in PEF 14–30 L/min; $p<0.0001$). Individual differences in PEF between the two devices could be >100 L/min. The FEV_1 values were slightly, but significantly, lower on the home spirometer (95% CI for difference in FEV_1 0.02–0.1 L; $p=0.0018$).

Conclusions

A home spirometer provides reproducible and quality acceptable measures in children with asthma when performed under professional supervision and encouragement. Mean PEF and FEV_1 values recorded on this home spirometer are significantly lower than those on a hospital pneumotachograph, and individual differences may be large. Therefore, home spirometry may not be interchanged with pneumotachography in a lung function laboratory.

Introduction

Lung function measurements, for example peak expiratory flow (PEF) and forced expiratory volume in the first second (FEV_1), are used world-wide in the treatment and follow-up of asthma in children and adults.[1-3] PEF is primarily a measure of the patency of large intrathoracic airways and is very dependent of the effort made by the patient, whilst FEV_1 is thought to reflect the calibre of medium-sized airways and is less effort dependent.[4,5] Spirometers have to meet quality criteria formulated by international boards, such as the American Thoracic Society (ATS), and have to be calibrated regularly.[5] Such lung function measurements mostly take place in hospitals and only provide a 'snapshot' impression of lung function in asthma. The characteristic variability in lung function can better be assessed by repeated home measurements of lung function.[1,2] In the past, this was done by using mechanical PEF meters and hand-written PEF-diaries.[6-8] Research has shown, however, that these are highly unreliable, and the use of home spirometers with electronic data logging has been advocated since.[9-11] In addition to their reliability, these electronic home spirometers have the advantage of measuring both PEF and FEV_1, which improves their profile as devices for monitoring asthma and are promising devices for lung function measurements at home. These portable electronic home spirometers meet the quality criteria based on computer-generated wave-forms.[3,5] However, studies have shown differences in quality of these devices and in quality of measurements when used in different target disease populations.[12-15] It is unclear whether lung function values derived from a validated portable home spirometer can be interchanged with lung function values derived from a hospital-based

pneumotachograph. Therefore, in addition to the physical validation, home spirometers need also be validated in vivo in the target disease population.[15]

This study was designed to assess the accuracy of an electronic home spirometer (Koko Peak Pro, Ferraris, Louisville, CO), in measuring PEF and FEV_1 in a population of schoolchildren with asthma in a hospital setting and was based on the observation in an earlier study that PEF and FEV_1, measured at home on this device, rendered lower values than both PEF and FEV_1 measurements on a pneumotachograph at the hospital.[16] Therefore, we compared PEF and FEV_1 values recorded on a home spirometer, with those obtained by the gold standard (on a hospital pneumotachograph), both under professional supervision and in a hospital setting.[1,2]

Methods

Children with mild to moderate persistent asthma visiting our outpatient clinic for lung function measurements were asked to participate in this study, which was approved by the hospital ethics review board. Patients and parents gave written informed consent. Children who had respiratory symptoms within 4 weeks before the measurements were excluded. The number of participants was based on an expected high correlation between the two devices, with a correlation coefficient >0.95, and on the objective to apply Bland–Altman plots to assess agreement between the two devices.[17] We predetermined the maximum clinically acceptable difference between the two measurements at 20 L/min for PEF and at 0.05 L for FEV_1 with an expected standard deviation of 50 L/min for PEF and 0.1 L for FEV_1, respectively. When using a criterion of significance of 0.05 and a minimum power of 80%, a total of 50 participants was needed.[17]

Lung function measurements were performed at our pulmonary function laboratory according to ATS guidelines.[5] All lung function measurements were supervised by a skilled technician who encouraged the children to perform optimal measurements on both devices.[5] Children were randomized, using Ranstam's block randomization into two groups.[18] One group performed PEF and FEV_1 on the electronic home spirometer (Koko Peak Pro) first and then on a Jaeger Masterlab pneumotachograph (Erich Jaeger, Würzburg, Germany); the other group performed measurements in

reverse order. A single new home spirometer (serial no. A004692B) was used in all measurements.[3,5] This is a home spirometer, in vitro validated by using computer-generated wave-forms which are based on precision and accuracy criteria form the ERS/ATS guidelines.[5] In both devices, maneuvers were performed in an upright position (head and neck remained straight). No computer animations were used. On the home spirometer, the best PEF and FEV_1 values from three reproducible measurements were automatically stored on the device's microchip. The microchip data were downloaded to a computer.

The number of maneuvers needed to obtain these three reproducible measurements and the actual PEF and FEV_1 values of all maneuvers were recorded separately. Both the children and the technician were blinded for the lung function values. Using the electronic home spirometer, measurements were regarded as being complete when the patient had executed three reproducible maneuvers with maximum effort, achieving PEF as rapidly as possible and continuing the maneuver for at least 2 sec, all judged by an experienced technician. With the hospital pneumotachograph, the best three reproducible flow-volume curves were selected by the technician. The number of maneuvers needed to obtain three reproducible measurements was recorded. Only the flow-volume curves were visible on the hospital spirometer display, not the corresponding PEF and FEV_1 values. As a result, the children and the technician were also blinded for these lung function values. After completing all maneuvers, the best PEF and FEV_1 values obtained from the three reproducible maneuvers on both the home spirometer and the pneumotachograph were judged using international quality criteria for reproducibility of maneuver performance (a minimum of three measurement values with a maximum difference of 10% or 24 L/min in PEF, whichever is greater, and a maximum difference of 5% or 0,1 L in FEV_1 measurements, whichever is greater).[3,5] For both PEF and FEV_1, reproducibility was calculated as the difference between the highest and the lowest of the three best values as a percentage of the mean value of the three best values.[5] All data were analyzed using PRISM™ (GraphPad Software, San Diego, CA) for Windows™ version 3.00 applying Bland–Altman plotting as appropriate.[17]

Results

Fifty children, aged 6–17 years, with stable mild to moderate persistent asthma entered and completed the study. Patient characteristics are shown in table 1. All children had performed technically sound and reproducible lung function measurements previously at our lung function laboratory.

All patients performed three reproducible lung function measurements with good effort which fulfilled international quality criteria.[5] Maneuver reproducibility on the home spirometer was 4.5% (95% confidence interval 3.8–5.2%) for PEF and 2.7% (95% confidence interval 2.3–3.2%) for FEV_1, with a mean difference between the highest and lowest of the three best measurements of 11.8L/min (95% confidence interval 9.9–13.6L/min) for PEF and 0.06L (95% confidence interval 0.05–0.07L) for FEV_1. The numbers of maneuvers needed to obtain these three reproducible recordings for both devices are shown in table 2.

Table 1. Patient characteristics

Sex (M/F)	66% versus 34%
Mean age (years)	10.8 ± 2.9
Maintenance medication:	
Inhaled corticosteroids	84%
Short-acting bronchodilators on demand	100%
Long-acting bronchodilators	46%
LTRA	none
Smoking parent(s)	none
Positive skin prick test or specific IgE to common inhalant allergens	76%
History of asthma in parent(s) or sibling(s)	56%
FEV_1 hospital spirometer (% predicted FEV_1)	100.7 ± 13.3

Values are presented as mean ± SD, or as percentage. M: male; F: female; LTRA: leukotriene receptor antagonists; FEV_1: forced expiratory volume in one second.

Table 2. Numbers of maneuvers needed		
	Pneumotachograph	Home spirometer
Number of maneuvers needed to obtain three reproducible measurements (the three included)	4.0 ± 0.9	5.6 ± 1.3

Values are presented as mean ± SD. The mean number of needed maneuvers was significantly different between the two devices (95%CI 1.2 to 2.1; p<0.0001). There was no significant difference between the randomized groups.

As expected, both PEF and FEV_1 showed a very high correlation between the two devices. The correlation coefficient for the PEF measurements between the devices was 0.95; for FEV_1, it was 0.99. However, PEF recorded on the home spirometer was significantly lower than on the hospital spirometer, with a mean difference of 22L/min (95% confidence interval for difference 14–30L/min; p<0.0001) (table 3). FEV_1 was also significantly different between the two devices, but the size of the difference was smaller (mean 0.06L; 95% confidence interval for difference 0.02–0.1L; p<0.05) (table 3).

Table 3. Spirometry Data		
	Mean ± SD	95% CI
Home spirometer		
Mean PEF (L/min)	278 ± 78	256–300
Mean FEV_1 (L)	2.35 ± 0.75	2.14–2.56
Pneumotachograph		
Mean PEF (L/min)	300 ± 91	274–326
Mean FEV_1 (L)	2.41 ± 0.79	2.19–2.63
Between devices		
Mean difference in PEF (L/min)	22 ± 29	14–30
Mean difference in FEV_1 (L)	0.06 ± 0.13	0.02–0.10

Mean spirometry data for the whole study population. PEF: peak expiratory flow; FEV_1: forced expiratory volume in the first second; SD: standard deviation.

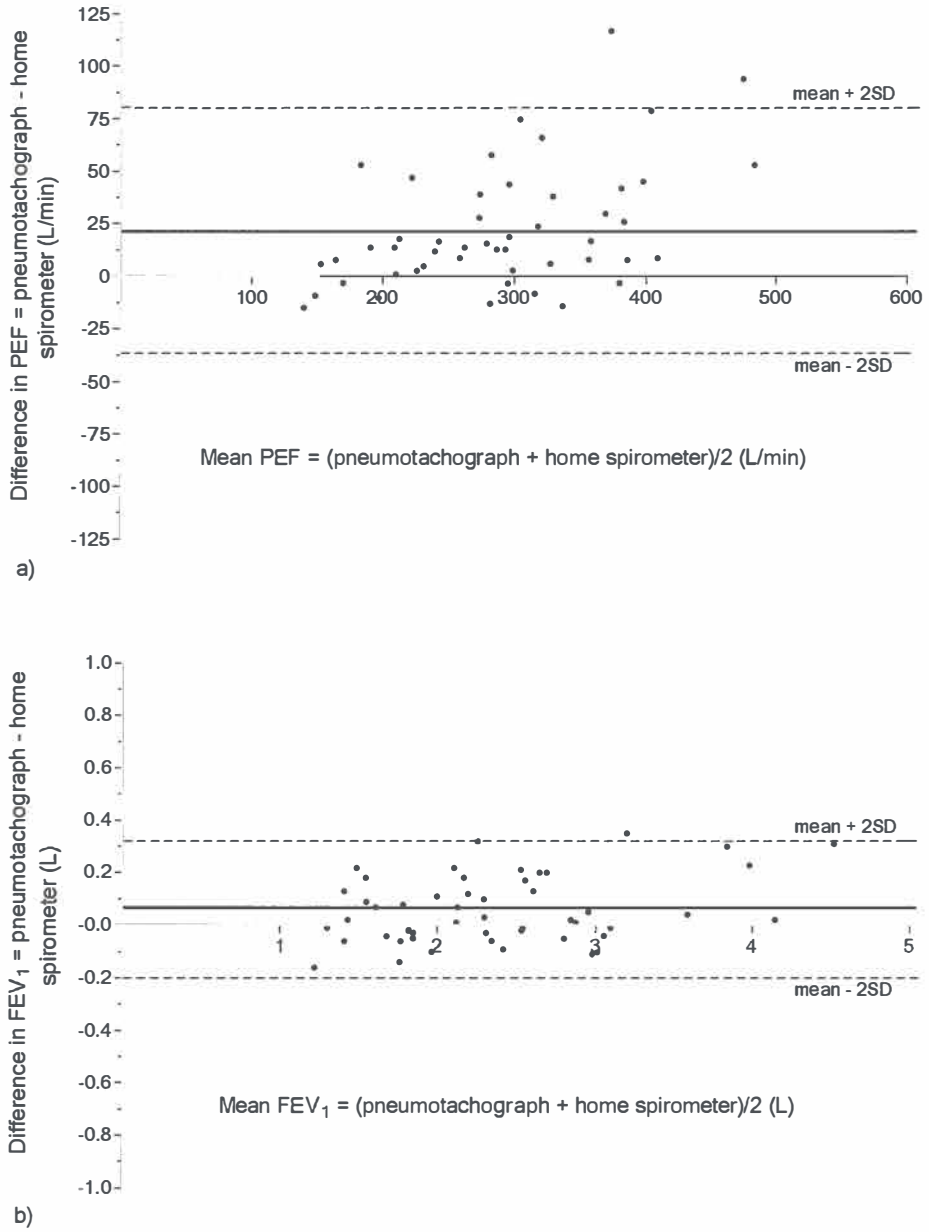

Figure 1ab. Bland-Altman plot of the difference in a) PEF (L/min) and b) FEV_1 (L) between the home spirometer and the hospital spirometer. The bold line represents the mean difference and the dotted lines the 2SD of the mean. FEV_1: forced expiratory volume in the first second; SD: standard deviation.

The Bland–Altman plots show the degree of agreement in PEF (fig. 1a) and FEV_1 (fig. 1b) between the two devices and the limits of agreement (mean±SD). These limits are 80 and -36L/min for PEF and 0.32 and -0.20L for FEV_1 and are higher than the predetermined clinically acceptable differences. Nearly 12% of the PEF values showed differences greater than 50L/min, and 7% greater than 75L/min between the two devices. For FEV_1, 19% of the differences between measurements were greater than 0.2L and 7% greater than 0.3L.

Discussion

This study shows that a portable home spirometer can provide reproducible and quality acceptable PEF and FEV_1 measurements in children with asthma, but that these measurements cannot be interchanged with measurements obtained with a pneumotachograph in a lung function laboratory. Both PEF and FEV_1 were significantly lower on the home spirometer than on the pneumotachograph. The size of their difference in PEF was large enough to be clinically relevant (22L/min, 95%CI 14–30L/min); the size of the difference in FEV_1 was smaller (0.06L; 95%CI 0.02–0.1L). Although the clinical relevance of the mean difference may be doubtful, several of the individual differences clearly were of clinical significance. Differences between the two devices in individual patients could be >100L/min for PEF and >0.25L for FEV_1, which are both clinically relevant. This suggests that PEF and FEV_1 recorded on this home spirometer are not valid proxies for PEF and FEV_1 recorded on a pneumotachograph in a lung function laboratory setting. It illustrates that even home spirometers which comply with ATS measurement criteria in vitro, should be validated in the patient group in which the device is to be used. This is in agreement with another study which found a clinically relevant difference in the quality of home spirometry measurements between populations from two different cities, with no suitable explanation.[15]

Home monitoring of lung function is considered important in the management of childhood asthma.[1,2] It has been shown that written PEF diaries are unreliable,[10] and the use of home spirometers with electronic data logging have been advocated to overcome this inaccuracy. [11] Studies using electronic home spirometry in childhood asthma, however, showed a highly variable relationship between home spirometry

measurements and asthma severity.[16] In addition, electronic home monitoring of lung function did not improve asthma control when compared to symptom-based self-management.[19] These observations raise the possibility that measurements obtained by home spirometry are inaccurate. This was addressed in the present study. Although the data in this study were derived from a single home spirometer and it may be different for other home spirometers, it is quite likely that any other home spirometer will also show a difference with professional pneumotachography.[12-14] We, therefore, prompt clinicians and researchers to examine the differences between measurements obtained on home spirometers intended for clinical use and those recorded in the lung function laboratory.

This home spirometer was validated according to ATS/ERS criteria,[5] which were revised after this study was undertaken.[20] In these revised guidelines, the test profiles remained unchanged, but requirement of new test profiles is advocated. Nevertheless, one should expect reasonable agreement between measurements obtained on any home spirometer and those recorded on a hospital pneumotachograph. We were rigorous in standardizing the measurements for both devices, strictly following ATS/ERS guidelines for measurement of lung function, including those for reproducibility of efforts.[5] For both devices, measurements were obtained under professional guidance and encouragement, thus eliminating the possibility of lower values due to suboptimal patient performance when such professional supervision is lacking.[3,5] Measurements were made in random order on both devices, eliminating bias by a 'learning' effect or by spirometer induced bronchoconstriction. Both the technician and the patient were blinded for the lung function values obtained. Therefore, the difference found between the two devices cannot be explained by different measurement conditions, but appear to be related to the device itself. It is likely that the lack of visual feedback on performance with the home spirometer used is the most important factor explaining the lower values obtained with the home spirometer. Home spirometers with a screen allowing visual feedback on the quality of flow-volume loops are being developed, but their measurement results have to be compared to a pneumotachograph in vivo.

In adults, it has been shown that the increased external resistance, associated with the measurement technique of a portable peak flow meter reduces PEF by up to 8%, when compared to a pneumotachograph.[21] This appears to be caused by the fact that PEF is reached slightly later in comparison to computer generated wave-

forms.[21] The home spirometer applied in this study measures air flow from the shifting of a thin metal plate. This may cause an increased resistance to airflow, the size of which remains to be determined. Finally, the lack of (daily) calibration possibilities on a home spirometer renders the measurements more susceptible to changes in ambient temperature, humidity and air pressure, than a pneumotachograph which is calibrated twice daily.[5]

Although this study shows that measurements obtained with an electronic home spirometer and with a professional pneumotachograph are not interchangeable, this does not necessarily render home spirometers useless. Our results clearly show that lung function measurements on an electronic home spirometer are highly reproducible, at least when performed under professional supervision and encouragement. This suggests that home spirometry can be used to calculate diurnal variation of lung function, or for tracking changes over time of lung function values measured with the same device.

Our study population consisted of well-controlled asthmatic children and it could be argued that the accuracy of home spirometry may be less in symptomatic patients. This study shows that reproducibility of PEF and FEV_1 measurements was not dependent on the level of PEF and FEV_1 values. However, because PEF in particular is dependent on the effort of the patient,[3] a patient having acute symptoms of asthma may have more difficulty to maintain optimal effort with a probably higher number of measurements needed than a patient with stable asthma.

In order to obtain high-quality measurements, home spirometers are equipped with quality notifications and incentives, including automatic notification of maneuver failure (when the maneuver is too short to measure FEV_1, or when PEF is not reached within preset limits) and a sound signal during the maneuver, or when it is completed. The home spirometer used in this study provides no incentives during the forced expiratory maneuvers, but does give a quality notification when PEF is not reached within preset limits.[3,5] Because both the technician and the patient were blinded for the outcome during the measurements, quality control, including maneuver reproducibility, had to be applied after completing the whole procedure. Even without quality notifications or incentives, the difference between FEV_1 on the home spirometer and the hospital spirometer measurements was clinically acceptable and within the limits set by international guidelines.[5] This is in

accordance with a previous study showing a high number of quality acceptable measures at home with no deterioration within 4 weeks using a similar device.[22]

The higher number of maneuvers needed on the home spirometer to obtain three reproducible measurements may show that a certain level of instruction, training, and perhaps even encouragement is needed to obtain sufficient reproducible measurements for clinical practice. Recently, it has been shown that training and education of patients are more important than encouragement to obtain reliable and consistent lung function measures using home spirometry over time.[15] However, we cannot rule out that the higher number of maneuvers on the home spirometer are due to the blinding of the technician and therefore being unsure at what moment the three optimal measurements were achieved. All our patients were experienced in performing lung function measurements. This may help to explain why the difference in measurements obtained by the two devices in our study was small. Clearly, children with asthma should be trained in performing forced expiratory maneuvers reliably and reproducibly before embarking on home spirometry. Under these circumstances, it has been shown that the quality of lung function measurements with home spirometry remains consistent over a period of 3 months.[15,18,22]

In conclusion, when children are well trained to perform forced expiratory maneuvers reliably and reproducibly, home spirometry with electronic data logging provides a fairly reliable measurement of FEV_1 in children with asthma. However, mean PEF and FEV_1 values recorded on this home spirometer are lower than those obtained by a hospital pneumotachograph, and individual differences in PEF and FEV_1 between the two devices may be large. Therefore, home spirometry and hospital pneumotachography should not be used interchangeably, because differences in the devices, including the lack of visual feedback on small portable home spirometers, may significantly influence the results in an important proportion of the patients.

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Chapter 3

Home spirometry and asthma severity in children

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Abstract

Background

The usefulness of peak expiratory flow monitoring is disputed because of the unreliability of written peak flow diaries. The aim of this study was to examine the relationship of peak flow and forced expiratory volume in one second (FEV_1) variation to other estimates of asthma severity in children, using an *electronic* home spirometer with automatic data storage.

Methods

Over a 3-month period, thirty-six children with mild to moderate persistent asthma recorded peak flow and FEV_1 electronically twice daily and an asthma severity score in a written diary. Bronchial responsiveness was assessed at the beginning and bronchodilator response and asthma specific quality of life at the end of the study.

Results

Peak flow variation correlated significantly, but weakly to bronchial responsiveness and bronchodilator response, but not to the asthma severity score or quality of life scores. Within individual correlations between asthma severity scores and home spirometry indices and between peak flow and FEV_1 were highly variable.

Conclusions

Peak flow and FEV_1 variation obtained by home spirometry show poor concordance with other indices of disease activity and with each other. This limits the usefulness of home spirometry in childhood asthma.

Introduction

International guidelines on the management of asthma stress the importance of pulmonary function tests to monitor the clinical course of asthma and to achieve optimal control.[1-3] Measurements of bronchial responsiveness (BR) provide an estimate of asthmatic airway inflammatory activity and can be used in monitoring childhood asthma.[1,3,4] A study in adults has shown that adjusting maintenance therapy based on BR measurements improves asthma control and reduces asthmatic airway inflammation.[4] However, the downside of BR measurements – and of pulmonary function tests in general – is that they have to be performed in hospital and that they only provide a snapshot impression of asthma status, rather than that they reflect the inherent variability of the disease.[1-3,5]

This variation of pulmonary function is considered to be one of the key characteristics of asthma.[1,2] Day-to-day home monitoring of peak expiratory flow (PEF) is thought to reflect this variability and is, therefore, recommended in guidelines as a monitoring tool.[6] Early studies have found a strong correlation between PEF variation and BR in adult asthmatics.[7,8] However, more recent studies have found a weaker relationship between PEF variation and BR in patients treated with inhaled corticosteroids.[9-12] In all studies on the relationship between PEF variation and other indices of asthma severity,[13-15] mechanical PEF meters and written PEF diaries were used. Several studies have shown that written PEF diaries are unreliable[16,17] and it has been suggested that using electronic home spirometers could overcome this drawback.[18] Before being able to use electronic home

spirometers in a asthma self-management, the usefulness of these instruments in accurately reflecting asthma severity should be investigated. Therefore, the present study was designed to examine the relationship of home measured PEF and forced expiratory volume in one second (FEV_1) and their variation, using an electronic home spirometer, to other parameters of asthma severity in children with chronic persistent asthma.

Patients and methods

Patients aged 6 -16 yrs with mild-to-moderate persistent asthma[1,2] were recruited at the current authors' outpatient clinic (Princess Amalia Children's Clinic, Isala klinieken, Zwolle, the Netherlands). All had been using maintenance therapy with inhaled corticosteroids in daily dosages ≤400μg/day (budesonide, beclomethasone) or ≤200μg/day (fluticasone) for ≥6 months and were able to perform pulmonary function measurements reproducibly.[3,5] Children who had used systemic corticosteroids <4 weeks before the start of the study were excluded. Written informed consent was obtained from all participants and their parents. The study was approved by the hospital ethics review board.

For characterization purposes, different lung function measurements were completed by these patients. Flow-volume-loops were performed on a Jaeger Masterlab pneumotachograph (Erich Jaeger, Würzburg, Germany), following ATS/ERS guidelines.[3,5] Short-acting bronchodilators and long-acting bronchodilators were withdrawn for 8 h and 24 h, respectively, prior to each session. At the start of the 3-month study period, the degree of bronchial responsiveness was assessed using a methacholine provocation test with the dosimeter method and results were expressed as the provocative dose of methacholine causing a 20% fall in FEV_1 (PD_{20}).[3,19] At the end of the 3-month period the patients performed flow-volume loops before and after inhalation of 800μg salbutamol to assess bronchodilator response.[5] Children aged ≥7 yrs, and one parent of each patient completed the validated Dutch versions of the disease specific Pediatric Asthma (Caregiver's) Quality of Life Questionnaire. Responses to these quality of life questionnaires were expressed on a seven-point Likert scale, higher scores reflecting better quality of life.[20,21]

At the first visit patients were instructed how to use the electronic portable spirometer (Koko Peak Pro, Ferraris, Louisville, Colorado, USA).[5,6,22] This home spirometer has been validated using a precision waveform generator (Pulmonary Waveform System; MH Custom Design and Mfg, Midval, UT, USA) demonstrating its agreement with performance standards as recommended by international guidelines.[5] Patients were instructed to perform three forced expiratory flow manoeuvres twice daily between 06:00 and 10:00 and between 18:00 and 22:00 throughout the study period. All instructions were given by the same skilled assistant, encouraging the children to obtain optimal lung function values. Patients were instructed to expire for ≥2 seconds and measurements were only accepted if forced vital capacity was more than FEV_1. The device automatically stored the highest of the three correctly performed PEFs on a microchip, along with the accompanying FEV_1.

Throughout the 3-month period, patients also recorded a validated asthma severity score on a continuous visual analogue scale twice daily in a written diary.[23] Score 0 represented the "worst possible state of their asthma" and score 10 the "sensation of having no asthma at all". Children were instructed to first score their perception of asthma severity, then perform the forced expiratory flow manoeuvres on their home spirometer and finally take their medication. Patients also recorded use of rescue bronchodilators in the diary, both as a measure of asthma stability at home and to identify and exclude lung-function values influenced by bronchodilator medication. In order to identify exacerbations of asthma, patients were instructed to return to the clinic if they felt their asthma symptoms could not be controlled with rescue bronchodilators. Such exacerbations and use of systemic corticosteroids were recorded in the diary. Once a month, data from the home spirometer were downloaded to a computer. After careful inspection following a predefined algorithm[24], recordings due to technical errors and unexplained outliers were excluded.[22] Adherence to the home recordings was calculated by comparing the number of recordings over ~13 weeks (180 recordings minus the technical errors) with the number of recordings actually obtained. The PEF and the asthma severity score were expressed as percentage of the personal best value (%PB) and the FEV_1 as percentage of the predicted value (%pred).[25] Variation of PEF (and of FEV_1) was expressed in terms of the size of the day's range (amplitude) as a percentage of the day's mean (ampl%mean).[13] These calculations of diurnal variation were only performed in children with an overall adherence with home spirometry of ≥80%, in

order to obtain reliable variation calculations. The Spearman rank correlation coefficient was applied as appropriate during data analysis.[26]

Results

In total, 42 children completed the study. The median overall adherence to home spirometry and symptom diary keeping was 91.5% and 98.7%, respectively. Six children were excluded because of an adherence with home spirometry of <80%. Technical errors accounted for <10% of the missing data. Clinical characteristics of the remaining 36 children are presented in table 1 and results of home spirometry and asthma severity scores in table 2.

Table 1. Characteristics of 36 asthmatic children completing the study with ≥80% adherence with home spirometry

Male/Female (n)		25/11
Age (yrs)		10.4 ± 2.5
Age of onset of asthma (yrs)		2.8 ± 2.1
Maintenance medication:	Inhaled corticosteroids (%)	100
	Short-acting bronchodilators on demand (%)	100
	Long-acting bronchodilators (%)	44
	LTRA (%)	0
Exacerbations requiring systemic corticosteroids (%)		0
Smoking parent(s) (%)		31
Positive skin prick test or specific IgE to common inhalant allergens (%)		89
History of asthma in parent(s) or sibling(s) (%)		78
logPD_{20}-methacholine (µg)		1.98 (1.28-2.91)
FEV_1 (% pred)		99.1 ± 12.6
QOL (children)[#] 0-7		6.0 ± 0.81
QOL (caregiver)[¶] 0-7		6.4 ± 0.48

Data are presented as mean ± SD, or as median (interquartile range) unless otherwise stated. LTRA: leukotriene receptor antagonists; Ig: immunoglobin ; PD_{20}-methacholine: dose of methacholine causing a 20% fall in forced expiratory volume in one second (FEV_1); %pred: % predicted; QOL: quality of life. [#]: disease-specific QOL of children ≥ 7 yrs old; [¶]: disease specific QOL of caregivers.

Table 2. Results of home spirometry and severity score measurements	
Home spirometry	
PEF (%PB)	81.4 ± 6.3
FEV_1 (%pred)	85.5 ± 15.5
vPEF (ampl/mean)	7.9 ± 3.4
$vFEV_1$ (ampl/mean)	9.5 ± 4.3
Symptom diary	
Use of rescue salbutamol[#]	0.5 ± 0.7
Asthma severity score (%PB)	83.4 ± 12.9

Values are presented as mean ± SD. PEF: peak expiratory flow; %PB: percentage of personal best value; FEV_1: forced expiratory volume in one second; %pred: percentage predicted; vPEF: variation in PEF; ampl/mean: size of day's range as a percentage of the day's mean; $vFEV_1$: variation in FEV_1. [#]: 100µg puffs/day.

The mean PEF variation (expressed as amplitude/mean) over the 3-month period correlated significantly to bronchial responsiveness (Spearman's rank correlation coefficient (r_s) =-0.43, p=0.009) and to bronchodilator response (expressed as a percentage of pre-bronchodilator FEV_1; r_s=0.34, p=0.04), but the scatter was wide (fig. 1). Mean PEF and FEV_1 variation did not show significant correlations to the asthma severity score, or the patient's quality of life (table 3).

Table 3. Correlations between home spirometry results and asthma severity measures				
	PD_{20} µg	Bronchodilator response[#]	Pediatric asthma QOL score	Asthma severity score[¶]
PEF (%PB)	0.35; p=0.04 (0.01 to 0.61)	-0.38; p=0.02 (-0.64 to -0.06)	-0.10; p=0.58 (-0.43 to 0.26)	0.08; p=0.64 (-0.26 to 0.41)
FEV_1 (%pred)	0.36; p=0.03 (0.02 to 0.61)	-0.42; p=0.01 (-0.66 to -0.09)	0.15; p=0.39 (-0.20 to 0.47)	0.06; p=0.76 (-0.28 to 0.39)
vPEF (ampl/mean)	-0.43; p=0.009 (-0.67 to -0.11)	0.34; p=0.04 (0.00 to 0.61)	-0.05; p=0.79 (-0.39 to 0.31)	-0.15; p=0.39 (-0.46 to 0.20)
$vFEV_1$ (ampl/mean)	-0.43; p=0.008 (-0.67 to -0.11)	0.14; p=0.41 (-0.20 to 0.46)	-0.15; p=0.41 (-0.47 to 0.21)	-0.32; p=0.06 (-0.59 to 0.02)

Data are presented as Spearman rank correlation coefficient; p-value (95% confidence interval). PD_{20}: dose of methacholine causing a 20% fall in forced expiratory volume in one second (FEV_1); %PB: percentage of personal best value; PEF: peak expiratory flow; %pred: percentage predicted; vPEF: variation in PEF; ampl/mean: size of day's range as a percentage of the day's mean; $vFEV_1$: variation in FEV_1. [#]: percentage of initial FEV_1; [¶]: %PB.

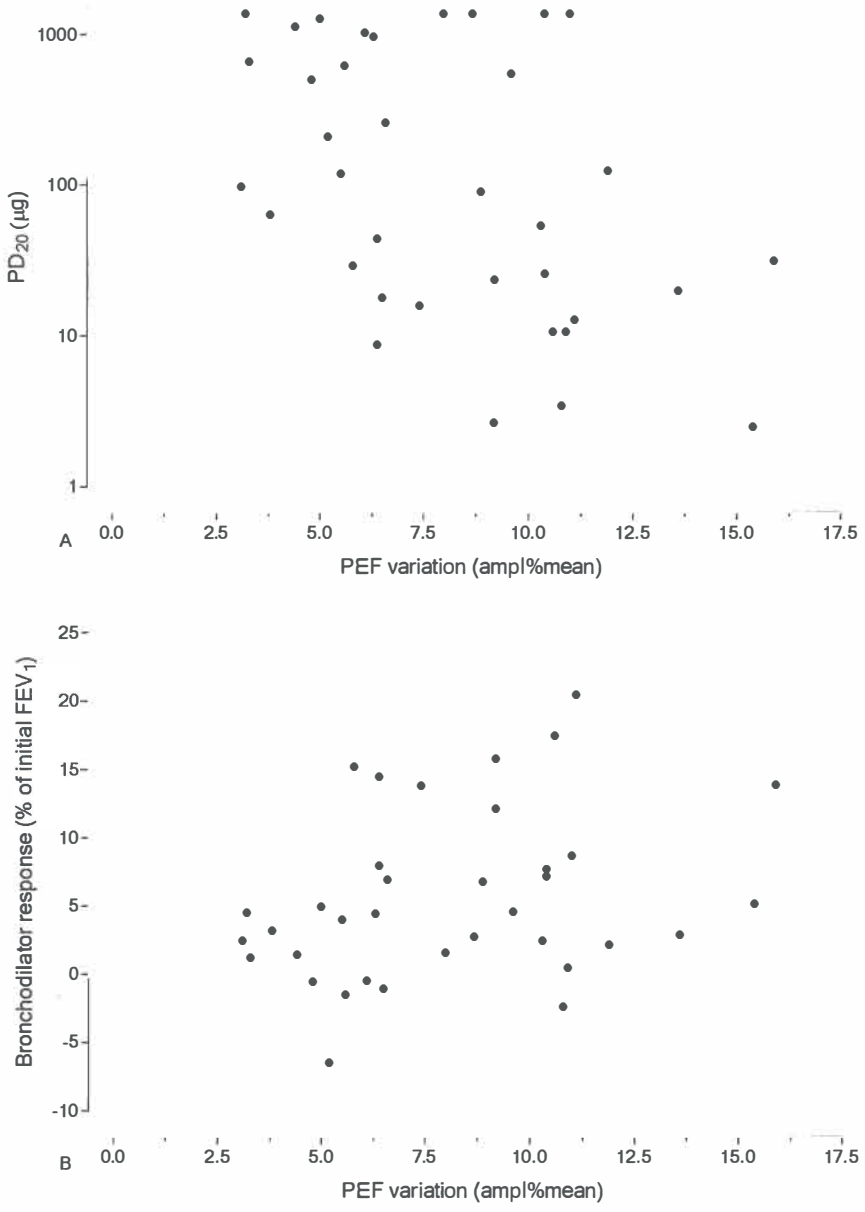

Figure 1AB. Correlation of peak expiratory flow (PEF) variation expressed as size of day's range as a percentage of the day's mean (ampl/mean) to A) dose of methacholine causing a 20% fall in forced expiratory volume in one second (FEV_1; PD_{20}) and B) bronchodilator response. Although the correlation is significant (Spearman's rank correlation coefficient (r_s) = -0.43; p=0.009 and r_s= 0.34; p=0.04) respectively), the scatter is wide.

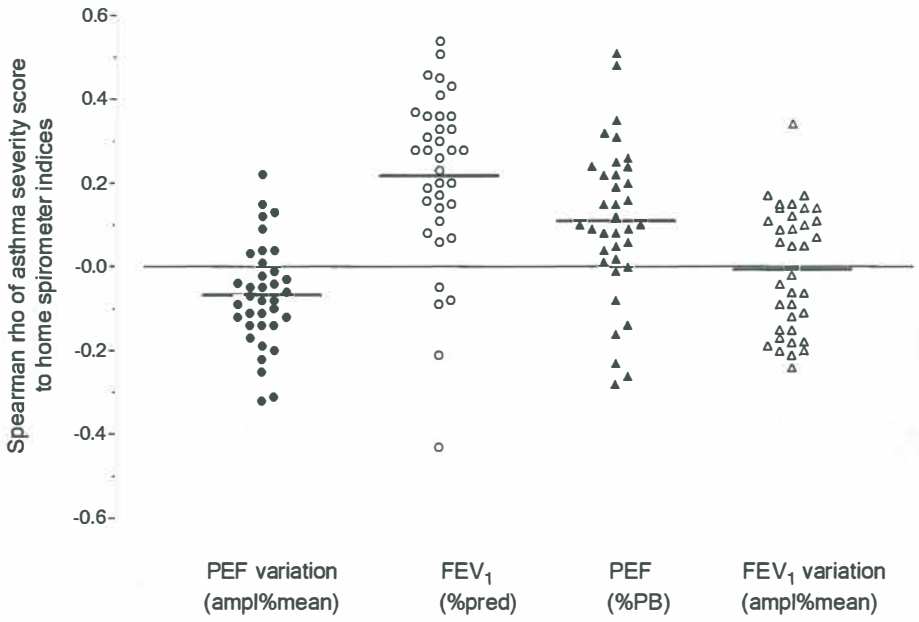

Figure 2. Distribution plots of individual Spearman's rank correlation coefficient correlations (r_s; one point per patient) of asthma severity score to peak expiratory flow (PEF) variation (expressed as size of day's range as a percentage of the day's mean (ampl/mean); ●), forced expiratory volume in one second (FEV_1; expressed as percentage of predicted value; ○), PEF (expressed as percentage of personal best; ▲) and FEV_1 variation (ampl/mean); △). ——: median values.

The correlations between the asthma severity score and home spirometry indices were highly variable in individual patients (fig. 2). For example, the individual correlation coefficients between asthma severity scores and corresponding FEV_1 values in individual patients ranged from -0.28 to 0.51, with a mean of 0.10.

Several examples of individual recordings of home spirometer indices and the asthma severity score are presented in figure 3. The most striking finding was the large variation between and within subjects in the relationships between PEF, FEV_1 and asthma severity scores. Increases in asthma severity scores were accompanied by decreases in PEF and FEV_1 values in some patients, but by increases in others.

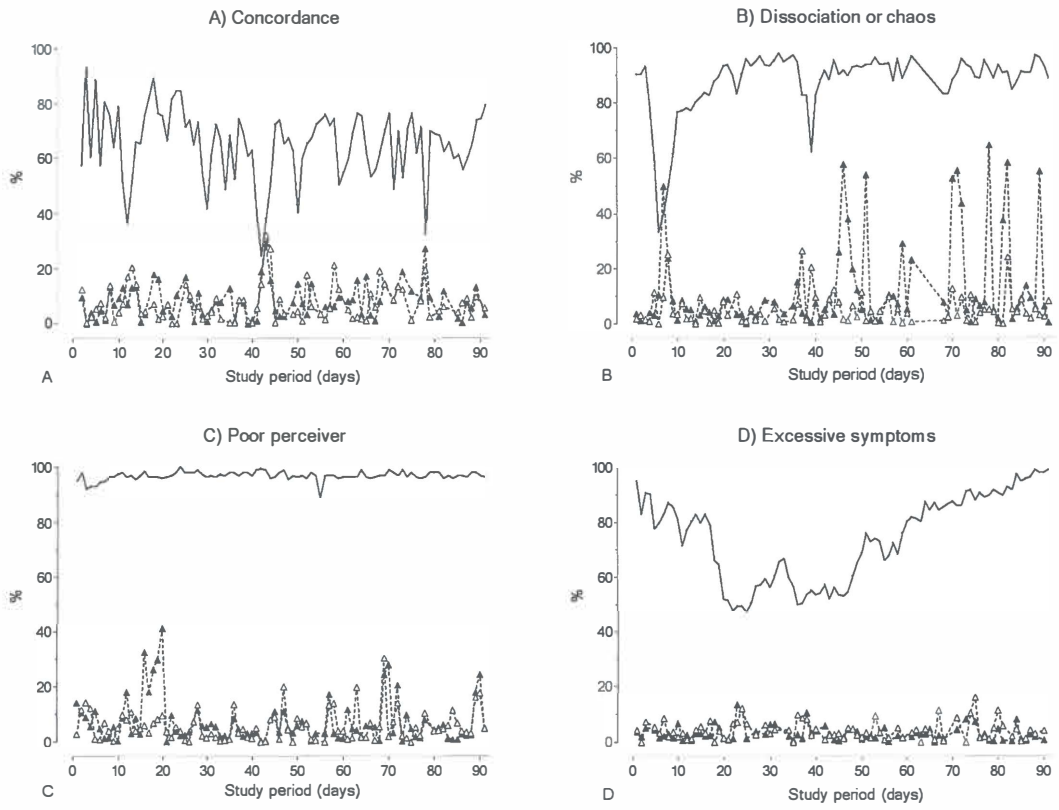

Figure 3. Samples of individual monitoring data showing four different patterns of relationships between asthma severity score, forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) variation. A): concordance of patients ; B): dissociation or chaos; C): poor perceiver; and D): excessive symptoms categories. ——: asthma severity score (percentage of personal best); Δ: PEF variation (expressed as size of day's range as a percentage of the day's mean (ampl/mean); ▲: FEV_1 variation (ampl/mean).

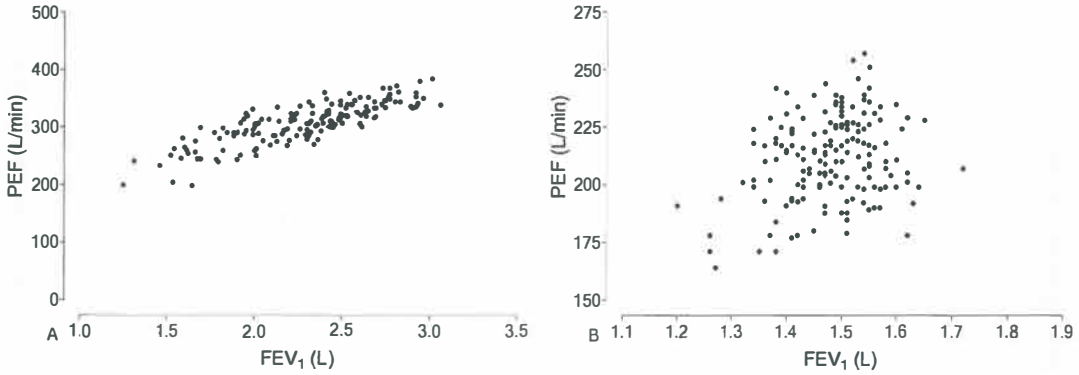

Figure 4. A) Concordance and B) discordance between measured peak expiratory flow (PEF) and accompanying forced expiratory volume in one second (FEV_1) in two individual patients.

Based on the association patterns between home spirometry results and asthma severity scores, the study group could be divided into four distinguishable patterns; reasonable concordance (n=7; 19.5%), dissociation or chaos (n=9; 25%), poor perceivers (n=13; 36%) and excessive symptoms (n=7; 19.5%; fig. 3) To the current authors' surprise, the concordance of PEF and FEV_1 values was highly variable between patients with only 67% of the patients showing an acceptable concordance (r_s >0.5; fig. 4)

Falls of PEF below 80% or below 60% of personal best values were accompanied by highly variable FEV_1 values (fig. 5). For example, although the mean FEV_1 associated with a PEF falling below 60% of the personal best value was 65.8%pred (95% confidence interval 63.9 to 67.8 %pred), the spread of FEV_1 values associated with this drop in PEF ranged from 18-120% of predicted values.

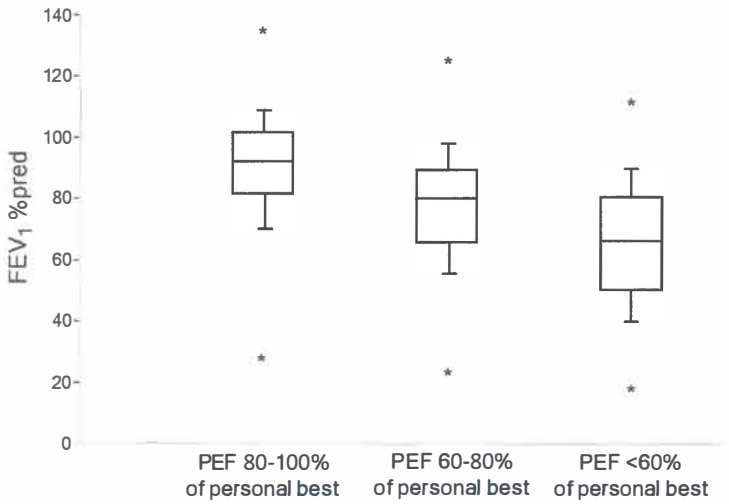

Figure 5. Box-and-whisker plots representing distributions of forced expiratory volume in one second (FEV_1) accompanying peak expiratory flow (PEF) values at 80-100% (n=4060), 60-80% (n=2162), and <60% (n=371) of personal best. Data are presented as medians, inter-quartile ranges and 90% ranges.*: minimal and maximal outliers.

Discussion

The current study shows that in asthmatic children, the correlation of electronically recorded PEF variation to other asthma parameters is too inconsistent to be clinically useful. This is not only true for PEF variation expressed as the amplitude as a percentage of the day's mean, but also for PEF expressed as a percentage of the personal best value and for the variation of FEV_1 (table 3). Although the unreliability of written PEF diaries is overcome by using an electronic home spirometer, this does not improve the poor concordance of PEF variation to other parameters of asthma severity.[11,12,27] The present authors propose that this poor concordance, both between and within patients, limits the usefulness of home spirometers in the monitoring and management of childhood asthma.

It is commonly stated that variation in pulmonary function is one of the key characteristics of asthma,[1,2] and that PEF variation reflects this variability.[6] In the present study, the variability of the subjective severity of disease was recorded daily using an asthma severity score which has been validated as accurate and reproducible.[23] Although PEF variation mirrored the variability of the asthma severity score in some patients, in most cases there appeared to be no relationship at all. In fact, 80% of subjects displayed a (complete) dissociation between indices of home spirometry and the asthma severity score (fig. 3). These findings concur with earlier studies using mechanical PEF meters.[27] Some of these patients may be regarded as "poor perceivers" with few symptoms despite considerable variation of PEF and FEV_1 and others as patients with excessive symptoms without any variation of PEF and FEV_1.[28] It would be interesting to see if poor perceivers, identified by home recordings, could benefit from stepping up therapy, but this study was not designed to answer that question.

Another striking finding of our study was the poor concordance of changes in PEF with changes in FEV_1, the gold standard of peripheral airways obstruction. Although overall correlation between PEF and FEV_1 is present and can be expected with properly performed manoeuvres, some individual patients show complete dissociation between PEF and FEV_1 (fig.4). Given the low use of rescue bronchodilators in the present study, it is highly unlikely that these findings were influenced by bronchodilators used during the day and before measurements.[29]

Similarly, falls of PEF below 80% or even below 60% of personal best values, which are commonly used as cut-off values for stepping up asthma therapy in self-management plans,[13] were accompanied by a wide range of drops in FEV_1 (fig. 5). This illustrates that PEF and FEV_1 are not interchangeable parameters of assessing airway obstruction.[6] FEV_1 is less dependent than PEF of the patient's effort and, consequently, is a better estimate of smaller airways obstruction.[5] Theoretically, therefore, monitoring FEV_1 could provide a more reliable assessment of airways obstruction than PEF. Possibly, the discordance between PEF and FEV_1 could, to some extent, be explained by FEV_1 being a better measure of smaller airway obstruction than PEF. In the current study, however, the relationship of FEV_1 variation to other parameters of disease activity was as variable as that of PEF variation (table 3).

The present findings can probably not be explained by poor accuracy or measurement characteristics of the home spirometers, which meet the performance standards recommended by international guidelines, both for PEF and for FEV_1.[5] Although it can be argued that measurements at home are not performed under supervision of a skilled assistant, who can encourage the children to obtain optimal recordings and who can provide visual feedback of correct performance by examining flow-volume loops or by using computer incentives or animations, it has been shown that the technical quality of home spirometry recordings in children is usually acceptable.[30] It is therefore, even more striking that very low FEV_1 levels may be encountered occasionally in children with chronic persistent, but clinically stable, asthma. (fig. 5) It can not be ruled out that some of these very low PEF and FEV_1 values were caused by poor lung function performance and lack of quality control at home. Lung function was, on average, normal in patients taking part in the current study (table 1).

Even though there were no exacerbations requiring oral corticosteroids in this study group throughout the 3-month period, PEF and FEV_1 values were highly variable in a number of patients (fig. 3). In such patients, FEV_1 values can drop as low as 18% of predicted, without being considered as technical errors or unexpected outliers according to predefined criteria.[24] As, in the context of this study, data recorded on the home spirometer were not used in a self-management setting as a basis for adjustment of therapy and were only analysed after completion of the 3-month study period, these low FEV_1 values did not prompt changes in asthma management immediately. If they had been used in such a setting, the poor concordance of FEV_1 and PEF (fig. 5) would have complicated self-management considerably. If a drop of PEF below 60% of personal best can be accompanied by FEV_1 levels ranging from 18-120% of predicted, it is quite unclear what the best approach to asthma management should be. At such a point in time, current self-management strategies suggest commencing oral steroids. Although this is logical with accompanying low FEV_1 levels, giving oral prednisolon to children with an accompanying FEV_1 of 120%pred is clearly inappropriate. Thus, monitoring both FEV_1 and PEF can be confusing when the changes in these two parameters are discordant. Similar findings have previously been described in adults with intermittent or mild persistent asthma[31], but not in children. The current study shows that such discordance occurs in as many as 33% of children with mild-to-moderate persistent asthma.

Asthma is a variable disease and although home spirometry appears to be a reliable and intuitively appealing way to monitor pulmonary function in children daily, the current study demonstrates that home spirometry in children with asthma shows highly variable relationships with several distinct measures of asthma severity, namely bronchial responsiveness, bronchodilator response, asthma severity scores and quality of life. In addition, peak expiratory flow values, obtained by home spirometry, show highly variable concordance to accompanying measurements of forced expiratory volume in one second. The results of the present study may help to explain why using an electronic home spirometer in self-management of childhood asthma does not appear to be useful in improving asthma control.[32] It is unlikely, therefore, that home spirometry is going to be useful in the long-term monitoring and management of childhood asthma.

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Chapter 4

Airway obstruction at time of symptoms prompting use of reliever therapy in children with asthma

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Acta Pædiatrica: Submitted.

Abstract

Background

In asthma treatment, doses of inhaled corticosteroids are often adapted to symptoms and need for bronchodilators. However, in cross-sectional studies in emergency room settings, lung function and respiratory symptoms are not always concordant. Available longitudinal data are based on written peak flow diaries, which are unreliable. Using home spirometry, we studied prospectively whether mild respiratory symptoms, prompting reliever therapy are accompanied by a clinically relevant drop in lung function in children with asthma.

Methods

For 8 weeks, children with asthma scored symptoms and measured PEF and FEV_1 on a home spirometer twice daily. Additional measurements were recorded when respiratory symptoms prompted them to use bronchodilators. Indices of home spirometry on symptom free days, days with respiratory symptoms and at times of symptoms were compared.

Results

50 children (mean age 9.5 yrs, range: 6-15; 31 boys) were included. The mean difference between symptom free days and at times of symptoms was 6.6% of personal best for PEF (95%CI 3.2 to 10.0; p=0.0004) and 6.0% of predicted for FEV_1 (95%CI 3.0 to 9.0; p=0.0004). There was complete overlap in PEF and FEV_1 distributions between symptom free days and at times of symptoms. The mean difference between symptom free days and days with respiratory symptoms was 3.2% (amplitude as % of mean) for PEF (95%CI 1.2 to 5.3; p=0.002) and 2.4% for FEV_1 (95%CI 0.2 to 4.5; p=0.03).

Conclusions

Although statistically significant, the degree of airway narrowing at times of respiratory symptoms, prompting the use of reliever therapy, is highly variable between patients, limiting the usefulness of home spirometry to monitor childhood asthma.

Introduction

Assessment of asthma control has become a key issue in current diagnosis and management guidelines of the disorder.[1,2] This assessment is largely based on the patient's perception of acute symptoms and the need for reliever therapy.[1,2] Studies have shown that many children with asthma as well as their parents are poor perceivers of airway obstruction,[3-5] and relying only on the patient's recognition of asthmatic symptoms may lead to both overtreatment or undertreatment.[4,5] This is why monitoring of lung function is advocated in asthma guidelines.[1,2]

As peak flow diaries have proven to be unreliable,[6] electronic home spirometers, measuring peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1), are increasingly being used to assess asthma control and to monitor treatment.[7-10] Studies have shown variable relationships of diurnal variation of lung function to daily symptom scores between children with asthma,[7-9] and even poor perception of airway narrowing during acute severe exacerbations in the emergency room.[10] However, whether mild but acute respiratory symptoms in asthmatic children at home, prompting them to take reliever medication, are accompanied by a measurable degree of bronchial obstruction, remains unclear. This is an important issue to clarify because such self-assessment of symptoms and the need for reliever medication form the basis of the asthma control scoring systems currently in use,[2] and are also used in treatment plans using adjustable dosing of asthma therapy.[11]

This study was designed to investigate whether mild respiratory symptoms, prompting the use of reliever therapy, are accompanied by a clinically relevant change in lung function, and thus whether schoolchildren with well-controlled asthma, using inhaled corticosteroids, perceive asthma symptoms adequately, when using bronchodilators at home.

Patients and methods

Children aged 6 to 16 years with mild to moderate persistent asthma, diagnosed by a pediatric pulmonologist,[1,2] and partly or well controlled on maintenance treatment with inhaled corticosteroids, were asked to participate in this observational study. Children using oral steroids within 4 weeks prior to the study, and those using long acting beta 2 agonists were excluded. The study was approved by the hospital ethics review board, a certified subsidiary of the Dutch central committee on research involving human subjects. All patients and parents provided written informed consent. Based on earlier studies, we estimated the average need for bronchodilators to be twice a week.[8,12] A study period of 8 weeks was assumed short enough to expect a high adherence and long enough to obtain a sufficient number of measurements per patient.[8,12]

A sample size calculation was performed as follows: in order to be able to detect a minimal difference of 5% in PEF (% of personal best; %PB) and FEV_1 (% of predicted value; %pred) between the daily morning and evening measurements and the measurements at time of symptoms that prompted the use of reliever therapy, assuming a standard deviation for differences of 10% for both PEF and FEV_1,[8] with an α of 0.05 and a power of 90%, a total of 44 data pairs were needed. In order to allow non-compliance or data errors, we aimed to include 50 patients.

Lung function measurements were performed on a Jaeger Masterlab pneumotachograph (Erich Jaeger, Würzburg, Germany), following ATS/ERS guidelines.[13] Short-acting bronchodilators were withdrawn for 8 hours prior to each session. At the start and at the end of the 8-week study period, patients performed flow-volume loops before and after inhalation of 800µg salbutamol to assess bronchodilator response. The fraction of nitric oxide in exhaled air (FeNO) was

measured at the start of the study using the portable NIOX MINO device, (Aerocrine, Solna, Sweden)[14] following international recommendations,[15] and expressed in parts per billion (ppb).

At the first visit patients were instructed how to use the electronic portable spirometer (Koko Peak Pro, Ferraris, Louisville, Colorado, USA).[13,16] This home spirometer has been validated both in vitro by using a precision waveform generator (Pulmonary Waveform System; MH Custom Design and Mfg, Midval, UT, USA), demonstrating its agreement with performance standards as recommended by international guidelines,[13] and in vivo in school-aged children with asthma.[17] Patients were instructed to perform three forced expiratory flow maneuvers twice daily between 6AM and 10AM and between 6PM and 10PM throughout the whole study period. In addition, children were asked to perform the same measurements at the moments that symptoms prompted them to take reliever inhalers (at time of symptoms). The device automatically stored the highest of the three correctly performed PEFs on a microchip, along with the accompanying FEV_1. All instructions were given by the same experienced technician, encouraging the children to obtain optimal lung function values. At least one parent attended the instruction session. Patients were instructed to achieve PEF as rapidly as possible and to continue the forced expiratory maneuver for at least 2 seconds. An integrated quality check warned the user by an exclamation mark when a cough was detected, the blow was not long enough, or there was a slow start. Patients were blinded to the measured lung function values by blacking out the display of the meter, leaving the exclamation mark and the integrated timepiece visible.

Twice daily throughout the 8-week period, patients scored their asthma symptom severity on a validated visual analogue scale in a written diary,[18] ranging from 0 (the "worst possible state of their asthma") to 10 (the "sensation of having no asthma at all"). This score was also recorded at time of symptoms prompting the use of reliever therapy. Time and date were recorded electronically on the memory chip of the home spirometer. Children were instructed to always record the asthma severity score on the visual analogue scale before performing the forced expiratory flow maneuvers on their home spirometer and taking their medication. In order to identify exacerbations of asthma, patients were instructed to return to the clinic if they felt their asthma symptoms could not be controlled with rescue bronchodilators.

Data analysis

After visual inspection following a predefined algorithm,[19] recordings due to technical errors and unexplained outliers were excluded. Measurements were only accepted for analysis if forced vital capacity exceeded FEV_1. Adherence to the home recordings was calculated by comparing the number of recordings expected over 8 weeks (112 recordings minus technical errors) to the number of recordings actually obtained. The PEF and the asthma severity score were expressed as percentage of the personal best value (%PB) and the FEV_1 as percentage of the predicted value (%pred).[20] Variation of PEF and of FEV_1 were expressed as the amplitude (maximum-minimum) as a percentage of the day's mean (ampl%mean).[21] PEF and FEV_1 values obtained during symptoms were only accepted when the time and date stamp were in agreement with the time and date noted in the diary. Assuming that the severity of the episodes with symptoms within the individual patient and between patients was comparable, a variable number of acute measurements should have no influence on analyses and interpretation of the data.[22] Asthma severity scores, PEF (%PB), and FEV_1 (%pred) obtained on days with respiratory symptoms were compared to values during symptom free days, and at time of symptoms.

Because self-management plans generally instruct patients to respond to a single drop of a level of lung function below a predetermined cut-off value,[2] there was the additional need to define such an 'event'. Therefore, the 1.5 SD below mean was calculated in each individual patient to identify asthma symptom score events (>1.5 SD below mean %PB), PEF events (>1.5 SD below mean %PB), and FEV_1 events (>1.5 SD below mean %pred).[23,24] This level of lung function reduction has proven to be more rigorous than the more commonly used drop to less than 80% personal best PEF.[23,24] The presence of such asthma severity score events and home spirometry events was assessed at times of symptoms, and their concordance was verified. Because not all children were expected to experience acute symptoms prompting use of reliever therapy, all morning and evening recordings from all children were also used to calculate the proportion of asthma severity score events accompanied by home spirometry events, as well as the proportion of home spirometry events accompanied by asthma severity score events.

Based on our earlier observation of four distinguishable association patterns between asthma severity scores and lung function variation assessed by home spirometry,[8] two independent pediatric chest physicians classified the recorded

patterns of daily symptom scores, PEF, and FEV_1 over time as reasonable concordance, chaos, poor perception or excessive symptoms. Inter-rater agreement was assessed by calculating Cohen's kappa statistic. All data were analyzed using PRISM™ (GraphPad Software, San Diego, California, USA) for Windows™ version 3.00 applying standard parametric and non-parametric tests as appropriate.[25]

Results

A total of 50 patients (31 boys) were included in this study, with a mean age of 9.5 (SD 2.2) years. All children had been using maintenance therapy with inhaled corticosteroids in daily dosages up to 400µg/day (budesonide, beclomethasone) or up to 200µg/day (fluticasone) for at least 6 months, and short-acting beta 2 agonists were used by all patients for relief of acute symptoms. All children were recruited from the population of asthmatic children followed up at our hospital-based pediatric asthma clinic. Three children (6%) also used leukotriene receptor antagonists; none used long-acting beta 2 agonists because this was an exclusion criterion for the study. All were able to perform pulmonary function measurements reproducibly.[13] Thirteen children (26%) were exposed to tobacco smoke at home, but all children denied smoking themselves. Forty children (80%) were sensitized to aero-allergens, mostly house dust mite and pets. Lung function characteristics are shown in table 1.

Table 1. Lung function characteristics of the 50 participating children at the start and the end of the study.

	At the start of the study (n=50)	At the end of the study (n=50)
FEV_1 (% pred)	95.5 ± 12.7	99.6 ± 12.2
Increase in FEV_1 (% pred) after 800 µg salbutamol	4.7 ± 4.3	5.3 ± 4.2
FVC (% pred)	99.9 ± 11.4	100.2 ± 10.8
MEF_{50} (% pred)	94.7 ± 28.2	90.4 ± 26.9
FeNO (ppb)	18.0 [13.0-25.0]	15 [12.0-26.0]

Data is presented as mean ± SD or median [Interquartile range]. FEV_1: forced expiratory volume in one second expressed as percentage of predicted value; FVC: forced vital capacity expressed as percentage of predicted value; MEF_{50}: maximal expiratory flow at 50% of the expiration expressed as percentage of predicted value; FeNO: fraction of exhaled nitric oxide expressed as parts per billion.

All children completed the study; one symptom diary contained no data so the analyses involving symptom scores comprised data from 49 children. During the 8-week study period, median adherence to home spirometry was 83.9% (Inter-quartile range (IQR) 67.0 to 92.0%) and the adherence to keep the symptom diary was 99.1% (IQR 96.0 to 100.0%). Less than 10% of non-adherence to home spirometry was based on incorrect and therefore unusable measurements. The remainder of the missing data was based on forgotten measurements, or measurements outside the given time frame. Thirty children (60%) had one or more days with respiratory symptoms requiring reliever therapy, comprising a total of 161 days (5.8%). From these 161 days, twenty-nine data points (18.0%) were excluded because of disagreement in time between the home spirometer and the symptom diary, notes in the diary without concurrent measurements or taking reliever therapy before the home spirometry measurement was performed. The remaining 132 data points were used for analysis. None of the children experienced an asthma exacerbation needing emergency care or systemic corticosteroids.

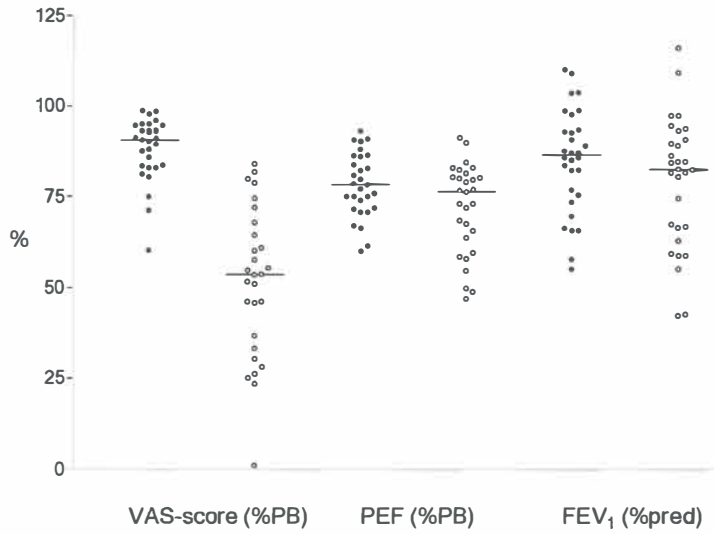

Figure 1. Home spirometry and symptom scores: Symptom free days compared to 'at times of symptoms'. ●: symptom free days; ○: at times of symptoms. VAS: visual analogue scale (asthma symptom score) expressed as percentage of personal best value; PEF: peak expiratory flow expressed as percentage of personal best value; FEV_1: forced expiratory volume in one second expressed as percentage of predicted value.

The symptom diary and home spirometry data comparing symptom free days to at times of symptoms are shown in figure 1. The mean difference between symptom free days and at times of symptoms was 36.2%PB for asthma severity score (95%CI of 29.3 to 43.2, p<0.0001), 6.6%PB for PEF (95%CI 3.2 to 10.0, p=0.0004) and 6.0%pred for FEV_1 (95%CI 3.0 to 9.0, p=0.0004). There was complete overlap in PEF and FEV_1 distributions between symptom free days and at times of symptoms, however (figure 1). While 71% of the times of symptoms prompting reliever therapy were identified as asthma severity score events (>1.5 SD below mean%PB), only 23.9% and 22.9% were scored as PEF events (>1.5 SD below mean%PB) and FEV_1 events (>1.5 SD below mean%pred), respectively. Moreover, the agreement of PEF and FEV_1 events was variable, as is shown in figure 2.

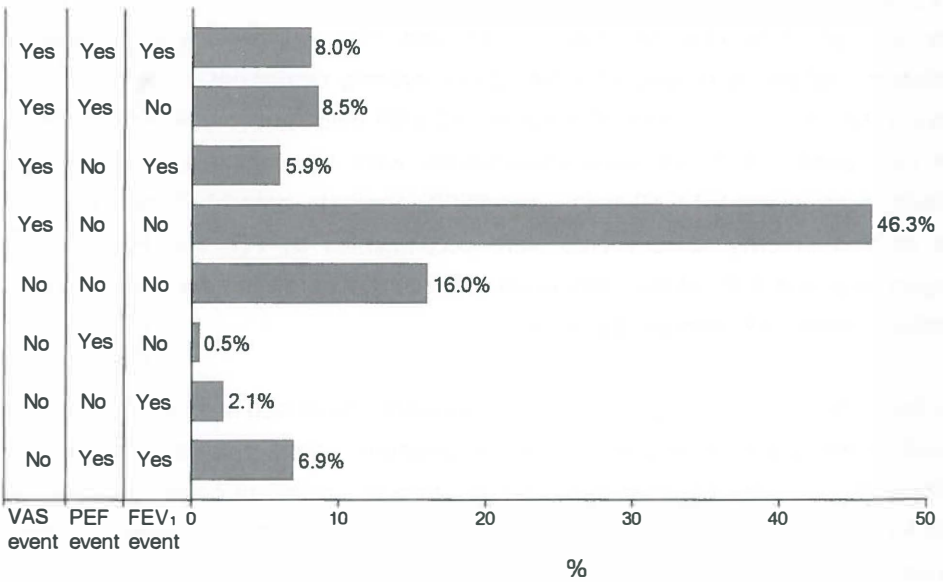

Figure 2. Presence of a fall in symptom score, PEF and/or FEV_1 1.5 SD below mean at times of symptoms, prompting reliever therapy. Data is presented as the percentage of the total number of times with respiratory symptoms prompting reliever therapy. VAS event: visual analogue scale (asthma severity score) >1.5 SD below the mean personal best value; PEF event: peak expiratory flow >1.5 SD below the mean personal best value; FEV_1 event: forced expiratory volume in one second >1.5 SD below the mean % predicted value. The figure does not add up to a 100% because there were no (reliable) home spirometry recordings available with an accompanying absence or presence of an asthma severity score event in 2.7% and 3.2 % of the times of symptoms, respectively.

Table 2. Mean asthma severity score and variation of lung function (vPEF and $vFEV_1$).

Home spirometry	Symptom free days (mean ± SD)	Days with respiratory symptoms (mean ± SD)	Mean difference (95%CI; p-value)
Mean VAS (% PB)	89.1 ± 14.0	73.1 ± 24.7	15.9 (14.0-17.8; p<0.0001)
vPEF (ampl%mean)	9.9 ± 10.9	13.2 ± 15.6	3.2 (1.2-5.3; p=0.002)
$vFEV_1$ (ampl%mean)	9.5 ± 11.3	11.8 ± 16.8	2.4 (0.2-4.5; p=0.03)

VAS: visual analogue scale (asthma severity score) expressed as percentage of personal best value; PEF: peak expiratory flow expressed as percentage of personal best value; FEV_1: forced expiratory volume in one second expressed as percentage of predicted value.

Table 2 shows the differences between days with respiratory symptoms and symptom free days in asthma severity scores and in the diurnal variation of PEF and FEV_1, again showing that the decrease in asthma severity scores was much larger than the accompanying decrease in PEF and FEV_1 on days with respiratory symptoms. When examining all morning and evening recordings in all patients in more detail, only 19.9% of the PEF events (>1.5 SD below mean%PB) and 16.9% of the FEV_1 events (>1.5 SD below mean%pred) were accompanied by an asthma severity score event (>1.5 SD below mean%PB). Similarly, only 14.6% and 11.4% of the asthma severity score events were accompanied by PEF and FEV_1 events, respectively, and 8.2% of the asthma severity score events were accompanied by a combination of a PEF and an FEV_1 event.

We found that the distribution of the four previously described association patterns, based on the graphical display of asthma symptoms scores and home spirometry recordings, was similar to that of our earlier study in a different patient group.[8] The two independent pediatric chest physicians only reached a fair agreement in their classification, however, with a kappa statistic of 0.37.

Despite considerable variation in individual patients, mean lung function on the home spirometer was comparable at the beginning and the end of the study period, with a mean difference in PEF of 0.8%PB (95%CI -4.2% to +2.6) and a mean difference in FEV_1 of 0.5%pred (95%CI -3.2% to +4.1) between the first and the last week of the study (table 1).

Discussion

This study shows that the degree of airway narrowing at times of respiratory symptoms, prompting the use of reliever therapy, is highly variable between children with asthma. Although mean PEF and FEV_1 were significantly lower at time of symptoms than on symptom free days, the difference was small (table 2), and the distributions of PEF and FEV_1 in individual patients showed complete overlap between symptom-free days and at time of symptoms (figure 1). Only some 20% of the PEF and FEV_1 measurements dropped below the predetermined 'event' level, while over two-thirds were assessed as asthma symptom score events at the same time. In addition, the concordance between PEF and FEV_1 events at times of symptoms was variable (figure 2). The degree of change in symptom scores at times these children decided to use their reliever therapy was much larger than the recorded drop in lung function (figure 1). Although this suggests that these children, as a group, use their bronchodilators more often than their home spirometry records seem to justify, there also was considerable variation between children in the relationship between symptom scores and lung function over time. Apparently, symptoms and home spirometry evaluate different aspects of asthma which do not always concur, and this relationship differs between patients. It proved difficult, however, to classify these patterns reliably between different experts. This highly variable relationship between symptoms, FEV_1 and PEF limits the usefulness of home spirometry in childhood asthma, because it remains unclear what change in which parameter the patient is expected to respond to, and whether this influences clinically relevant outcomes.

Home or hospital PEF measurements are of limited use because they are dependent on the patient's effort and because they mainly reflect large airway caliber instead of the increased small airways resistance characteristic of asthma.[4] Electronic portable spirometers have the advantage of being able to measure FEV_1 which is a more sensitive measure of asthma severity than PEF.[9,10] In previous studies, FEV_1 was more likely than PEF to identify a deterioration of lung function that children did not report,[9] and to demonstrate increased severity of exacerbations in an emergency room setting.[10] Conversely, in our study where children recorded PEF and FEV_1 on symptom-free days and at times of symptoms prompting them to take reliever medication, we found a similar variation and decrease in PEF and FEV_1 at

times of respiratory symptoms. Although the variable concordance between PEF and FEV_1 at times of respiratory symptoms confirms previous observations that these are not interchangeable parameters to measure airways obstruction,[13] the relationship between FEV_1 and asthma symptoms scores showed the same poor concordance as the relationship between PEF and asthma symptoms scores at times of symptoms. The approach used closely reflects the use of home spirometry as a monitoring tool in outpatients with asthma. Our study, therefore, provides no evidence that home spirometry FEV_1 measurements are more useful than home spirometry PEF measurements for home monitoring purposes.

Some limitations of the present study need to be discussed. Firstly, the quality of data obtained by home spirometry must be considered. Previous studies have consistently shown that home spirometry provides reproducible and technically reliably results,[26-28] although they are slightly lower than those obtained by hospital spirometry.[17]

Secondly, the symptoms that prompted patients to take reliever therapy were not specified, and may have included nonspecific complaints such as cough or breathlessness. This was a deliberate choice to reflect common clinical practice. In theory, different kinds of symptoms may be associated with different degrees of airway obstruction but this has never been substantiated. Apparently, asthmatic children take reliever therapy as needed, regardless of the nature of the symptoms, and this does not always reflect a clinically relevant degree of airway obstruction.

In addition, the selection of patients in our study needs to be considered. We deliberately intended to include patients with stable, well or partly controlled, mild-to-moderate persistent asthma for a number of reasons. First, this patient profile covers the majority of children with asthma in secondary care settings. Most of these children, although referred for poorly controlled asthma despite the use of inhaled corticosteroids, attain good asthma control [29] and normal levels of lung function [30] once they have been educated and trained extensively, and are being followed up closely, as has been noticed by others.[31,32] Still, these patients experience asthmatic symptoms from time to time, prompting the use of reliever therapy. It is important to study the reliability of such symptoms, because they form the basis of asthma control scoring systems used in clinical guidelines [2] and are being used increasingly in treatment strategies of variable dosing of asthma medication.[11]

Although including patients with more severe, difficult to control asthma, would have increased the number of symptom events, this would not necessarily have helped to elucidate the relationship between symptoms and lung function at times of respiratory symptoms prompting reliever therapy.

A final limitation concerns the timing of the measurements. Although the asthma severity scoring system has been validated as being reproducible and accurate,[18] the exact timing of symptom scoring was neither standardized nor controlled. The same limitation applies to timing of taking the reliever medication. Therefore, a certain degree of discrepancy in timing of symptoms and lung function measurements cannot be excluded, and this argues for some caution in interpreting our results. We tried to minimize this by clear and explicit instructions to patients and parents and by strictly excluding – a relatively large number of – evident disagreements between data points from the home spirometry and the symptom diary. In our earlier study, participants showed high adherence to home monitoring instructions during a 3-month study period, and were enthusiastic and eager to record reliable data.[8]

In the present study, the patients' own decision to take inhaled bronchodilators was used as the moment of assessing asthma severity scores and home spirometry recordings. Previous studies examining the relationship between symptoms and level of lung function have either been performed in emergency room settings, or have analyzed data recorded twice daily at fixed time points, but not at times of respiratory symptoms. Our approach was unique, therefore, and it showed that patients showed highly variable associations between symptoms scores, PEF, and FEV_1 at times they felt they needed reliever therapy. It showed that in only 8.0% of the times that bronchodilators were used, asthma symptoms, PEF and FEV_1 were fully concordant. Although a significant change in symptoms scores could be expected at times of symptoms, prompting the use of reliever therapy, symptom scores did not drop 1.5 SD below mean on more than 25% of occasions when bronchodilators were used (figure 2). Because more than one-third of these events were accompanied by a home spirometry event, it is unlikely that this was due to a too rigorously chosen cut-off value for symptom events.

In an attempt to identify children with poor symptom perception and excessive symptoms, the relationships of asthma symptoms and home spirometry recordings in time were assessed. The inter-rater agreement of the classification system used

was fair. Although identifying poor perceivers and patients with excessive symptoms would be clinically useful and may help to predict functional morbidity of asthma in children,[9] performing such a classification of patients based on home spirometry and symptom records may not be as straightforward and repeatable between observers as one might think. Further studies are needed to develop a more robust classification system of poor perception and excessive symptoms. Meanwhile, clinicians should be aware that the relationship between symptoms of asthma and lung function variation over time is highly variable between patients, and can be chaotic and erratic in many. As long as it remains unclear to what changes in symptom scores, PEF, or FEV_1 patients should respond to in which way, home spirometry is unlikely to be useful as a monitoring tool in children with asthma using inhaled corticosteroids. This is supported by evidence from clinical trials that self-management plans based on home recordings of lung function, even by electronic portable spirometers, is not superior to self-management based on symptoms alone.[33-35]

To our knowledge, this study is the first to examine the course of home-measured PEF and FEV_1 longitudinally over time, both on symptom free days and at times of acute respiratory symptoms prompting children to take reliever medication, without interference or assessment by a healthcare provider. It shows that the degree of airway narrowing at times of respiratory symptoms, prompting the use of reliever therapy, is highly variable. Classifying children as poor perceivers or as patients with excessive symptoms based on graphical display of home recordings of PEF, FEV_1, and respiratory symptoms proved difficult, with only fair agreement between observers. In many children, the association between symptoms and lung function variation on a daily basis is chaotic and erratic. These findings limit the usefulness of home spirometry in monitoring children with asthma in clinical practice.

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Chapter 5

Reference values for peak flow and FEV_1 variation in healthy schoolchildren, using home spirometry

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Abstract

Background

Current reference values for diurnal peak flow variation in healthy children (median 8.2%; 95th percentile 31%) are so high that considerable overlap exists with asthmatic children. These values have been obtained with written peak flow diaries, which are unreliable.

Aim

To obtain reliable reference values of peak flow variation and forced expiratory volume in the 1st second (FEV_1) variation in healthy schoolchildren using home spirometry with electronic data storage.

Methods

Healthy schoolchildren (n=204; 100 males), aged 6-16 yrs, measured peak flow and FEV_1 twice daily for two weeks using an electronic home spirometer. Variation of peak flow and FEV_1 were calculated as diurnal amplitude as a percentage of the day's mean.

Results

The mean peak flow variation was 6.2% (95th percentile 12.3%) and mean FEV_1 variation was 5.7% (95th percentile 11.8%).

Conclusions

Using home spirometry with electronic data storage, healthy schoolchildren show considerably less peak flow and forced expiratory volume in one second variation than previously reported with written peak flow diaries. Being the 95th percentiles of the distributions in healthy children, a peak flow variation of 12.3% and a forced expiratory volume in one second variation of 11.8% are suggested as cut-off values for disease when using home spirometry.

Introduction

Home monitoring of peak expiratory flow (PEF) is advocated in international guidelines for the management of asthma in children and adults.[1] Since PEFs are highly variable between patients, the patient's personal best value and diurnal variation in PEF are used in asthma guidelines, rather than age and sex dependent reference values for PEF levels.[2-5] Studies have shown a strong correlation between airway hyperresponsiveness and diurnal PEF variation in children with asthma.[6,7] Therefore, variation of PEF is considered to be a measure of asthma severity,[1,2] and a diurnal variation of PEF of >15-20% is considered increased. There is, however, only limited evidence to support this cut-off point.[1,2,8,9] The only reference values for PEF variation published have been obtained using mechanical PEF-meters with written diaries and showed high levels of PEF variation in healthy children, with a median of 8.2% and a 95th percentile as high as 31%.[9] As a result, PEF variation is regarded to be of limited use in the diagnosis of asthma in children.[1]

More recently, it was shown that recording PEF using written PEF diaries yields unreliable data and electronic recording was advocated.[10-12] Since the previously published PEF variation reference values were obtained using written PEF diaries[9], it is likely that these are unreliable. Children show high adherence to electronic home spirometry and perform these measurements in a technically correct manner.[13-15] The present authors hypothesised that values in records of diurnal variation of lung function in healthy schoolchildren obtained by electronic home spirometry would be lower than those recorded using unreliable written diaries of measurements from

mechanical devices. Therefore, the present study was designed to obtain new reference values for PEF variation and forced expiratory volume in one second (FEV_1) variation in healthy schoolchildren, using such a home spirometer with electronic data storage under field conditions.

Methods

Healthy peers, aged 6-16 yrs, of children with asthma visiting an outpatient clinic (Isala klinieken, Zwolle, the Netherlands), were recruited. Children were excluded if they had: 1) a recent or chronic disease of the respiratory tract, or a history of chronic respiratory disease; 2) a history of severe respiratory disease *e.g.* congenital lung disease, hospitalization for pneumonia or surgery of the thorax; 3) systemic disease with direct or indirect influence on the respiratory tract *e.g.* neuro-muscular disorders; 4) other chronic or acute disease with influence on the respiratory tract; 5) use of inhaled corticosteroids, bronchodilators or other medicines influencing the respiratory tract or 6) household exposure to tobacco smoke.[16]

In order to obtain PEF and FEV_1 variation data from different age groups and sexes, the intention was to include four groups, each of >50 children: males aged 6-11 yrs, males aged 12-16 yrs, females aged 6-11 yrs and females aged 12-16 yrs. The total number of 200 participants was preset empirically, based on previously published normative data studies concerning respiratory disease in childhood.[17-20] The age groups were formed to represent primary *versus* secondary schoolchildren.

At the start of the study, children performed flow-volume curves, in a pulmonary function laboratory (Isala klinieken), using a Jaeger Masterlab pneumotachograph (Erich Jaeger, Würzburg, Germany) following American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines for measuring lung function.[5] Children were excluded if their FEV_1 was <80% of the predicted value or the flow-volume curve had an abnormal shape.[5;21]

After inclusion, patients were instructed how to use the electronic home spirometer (Koko Peak Pro, Ferraris, Louisville, Colorado, USA).[1;5] This portable home spirometer has been designed to measure PEF and FEV_1 under field conditions without the need

for repeated calibration. It has been validated using a precision waveform generator demonstrating its agreement with performance standards as recommended by international guidelines[5;22], as well as in children with asthma in the same age group.[23] Patients were instructed to perform three forced expiratory flow manoeuvres twice daily at home between 06:00 and 10:00 and between 18:00 and 22:00 throughout a 2-week study period. All instructions were given by the same experienced technician, encouraging the children to obtain optimal lung function values and at least one parent attended the instruction session. Patients were instructed to achieve PEF as rapidly as possible and to continue the manoeuvre for ≥2s. An integrated quality check warned the user when a cough was detected, the blow was not long enough, or there was a slow start. The device then showed an exclamation mark and children were asked to repeat their measurements. During analyses, measurements were only accepted if forced vital capacity exceeded FEV_1. The device automatically stored the highest of the three correctly performed PEF measurements on a microchip, along with the accompanying FEV_1, labelled with the time and date of the measurement.

Following the 2-week study period, the device was returned and all records were downloaded on a computer. Adherence to home spirometry measurements was expressed as the percentage of days with two usable recordings (one recording in the morning and one in the evening).[24] Diurnal variation in PEF (in litres per minute) and in FEV_1 (in litres) were expressed as the absolute amplitude (maximum to minimum) as a percentage of the day's absolute mean (ampl/mean) and day-to-day variation in PEF and FEV_1 were expressed as the absolute amplitude (maximum to minimum) of the morning measurements as a percentage of their absolute mean (ampl/mean).[25]

All data were analyzed applying standard parametric and nonparametric tests as appropriate.[26] The present study was approved by the Medical and Ethical Judging Committee of the Isala klinieken, and study subjects and parents gave written informed consent. The reference values for PEF and FEV_1 variation obtained in the present population of healthy schoolchildren were compared to previously published results obtained in a sample of asthmatic schoolchildren over a 2-week period.[14] The home spirometer used, the instructions and procedures of recording PEF and FEV_1 at home, and the analysis of data were identical between the two studies.

Results

Healthy children aged 6-16 yrs (n=205), were included in the present study. After inclusion, one child was excluded because of abnormal lung function results and an abnormal flow-volume curve (FEV_1 <80%pred and curve concavity) at the start of the study, despite the absence of respiratory symptoms. Each predefined group consisted of ≥50 children, with a minimum number of 13 children per age year group. The characteristics of these groups are shown in table 1.

Table 1. Characteristics of the four age/sex groups

	6-11 yr olds		12-16 yr olds	
	Female	Male	Female	Male
Participants n	51	50	53	50
Age yrs	8.4 ± 1.7	8.8 ± 1.6	13.8 ± 1.4	13.7 ± 1.1
Pneumo % pred				
FEV_1	105.0 ± 11.9	103.9 ± 12.2	106.1 ± 10.9	98.5 ± 11.1
FVC	98.2 ± 11.1	98.9 ± 11.1	98.3 ± 11.4	92.8 ± 10.2
MEF_{50}	90.7 ± 20.3	88.7 ± 18.5	99.7 ± 19.2	93.7 ± 20.7

Data are presented as mean±SD, unless otherwise stated. Pneumo: pneumotachography; % pred: % predicted; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; MEF_{50}: mean expiratory flow when 50% of the FVC remains to be exhaled.

Table 2. Reference values for diurnal variation of peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1) using home spirometry with electronic data storage.

	Amplitude of variation % mean			
	PEF		FEV_1	
Age/sex groups	Mean (95%CI)	95th percentile	Mean (95%CI)	95th percentile
6-11 yr olds				
Female (n=51)	7.3 (6.4-8.2)	12.3	6.1 (5.4-6.8)	11.8
Male (n=50)	6.9 (6.1-7.7)	10.4	6.6 (5.8-7.4)	9.8
12-16 yr olds				
Female (n=53)	5.8 (5.0-6.7)	12.2	5.2 (4.5-5.9)	8.5
Male (n=50)	4.9 (4.3-5.6)	8.0	5.1 (4.3-6.0)	10.1
Total (n=204)	6.2 (5.8-6.7)	12.3	5.7 (5.4-6.1)	11.8

CI: confidence interval.

Table 3. Reference values for day-to-day variability of morning peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1) using home spirometry with electronic data storage. PEF and FEV_1 using home spirometry with electronic data storage.

	Amplitude of variation % mean			
	PEF		FEV_1	
Age/sex groups	Mean (95%CI)	95th percentile	Mean (95%CI)	95th percentile
6-11 yr olds				
Female (n=51)	7.3 (6.1-8.4)	12.2	7.1 (5.7-8.7)	13.2
Male (n=50)	6.8 (6.1-7.6)	11.3	7.0 (6.0-7.9)	11.3
12-16 yr olds				
Female (n=53)	5.8 (5.1-6.5)	8.7	5.3 (4.7-6.0)	8.6
Male (n=50)	5.2 (4.4-5.9)	9.5	4.8 (3.9-5.7)	8.7
Total (n=204)	6.3 (5.8-6.7)	12.2	6.1 (5.5-6.5)	11.3

CI: confidence interval.

The median adherence to home spirometry was 86%, with no significant difference between the groups and a small, but statistically significant difference between the first and the last week for the total study group (87 vs 82%; $p<0.0001$). The mean diurnal and day-to-day variation (with their 95th percentiles) in PEF and FEV_1, respectively, are shown in tables 2 and 3.

Children aged 6-11 yrs exhibited significantly higher variations of PEF (95%confidence interval (CI) for difference 0.9 to 2.5%; $p<0.0001$) and FEV_1 (95%CI for difference 0.5 to 2.0%; $p=0.002$) than children aged 12-16 yrs. There were no significant differences in variation of PEF or FEV_1 between males and females, nor between the first and the last week of measurements. Figure 1 shows the diurnal variation of PEF and FEV_1 per yr of age and illustrates the slightly decreasing variation of PEF with increasing age.

Both PEF and FEV_1 variation were independent of height and weight. Self-reported atopy was only present in six children. Exclusion of these six children did not change the outcome. None of the children showed a variation in PEF or FEV_1 of >20%. The overall mean diurnal PEF variation for healthy children aged 6-16 yrs was 6.2% (95%CI 5.8 to 6.7%; 95th percentile 12.3%), and the overall mean diurnal FEV_1

variation was 5.7% (95%CI 5.4 to 6.1%; 95th percentile 11.8%). The mean±SD absolute difference between the morning and evening PEF was 18.9±9.0 L/min (95%CI 17.7 to 20.2 L/min), and the mean absolute difference between the morning and evening FEV_1 0.13±0.07 L (95%CI 0.12 to 0.14 L). The diurnal differences between the age groups are presented in table 4. Of the healthy children, 76% exhibited a lower morning than evening PEFs, suggesting a similar circadian rhythm to that seen in asthmatic children.[27] However, only 48% of the healthy children showed a lower morning than evening FEV_1.

The previously published asthmatic group consisted of 36 well-controlled asthmatic children (25 males) with a mean age of 10.4 yrs.[14] In all of the children, the diagnosis was confirmed by a paediatric pulmonologist, and all were using maintenance treatment with inhaled corticosteroids. Their lung function characteristics are shown in table 5. Figure 2 shows the differences in PEF and FEV_1 variation between the well-controlled asthmatic children of the previously conducted study[14], and the present healthy children. The differences were significant for both diurnal PEF variation (p=0.001) and diurnal FEV_1 variation (p<0.0001), with mean differences of 1.4% (95%CI 0.3 to 2.5%) and 2.7% (95%CI 1.6 to 3.8), respectively. There was considerable overlap between the healthy children and the well-controlled asthmatics for both variables (fig. 2). The range of mean amplitude of diurnal PEF variation and diurnal FEV_1 variation in the asthmatic group was 3.5-24.3% mean and 2.8-26.4% mean for PEF and FEV_1, respectively, during the first 2 weeks of the study. Of the asthmatic children, 24 (62%) showed a diurnal PEF variation of >12.3% or a diurnal FEV_1 variation >11.8%, the overall 95th percentile of the healthy group of schoolchildren, in any given week of the total 3-month study period.

Table 4. Mean differences between the morning and evening peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1) using home spirometry with electronic data storage.

Age/sex groups	PEF L/min	FEV_1 L
6-11 yr olds		
Female (n=51)	16.4±5.6 (14.8-18.0)	0.10±0.04 (0.09-0.11)
Male (n=50)	17.5±7.7 (15.4-19.7)	0.12±0.06 (0.11-0.14)
12-16 yr olds		
Female (n=53)	23.5±13.0 (19.9-27.1)	0.16±0.08 (0.13-0.18)
Male yrs (n=50)	18.2±5.8 (16.5-19.8)	0.14±0.09 (0.12-0.17)

Data are represented as mean±SD (95% confidence interval), unless otherwise stated.

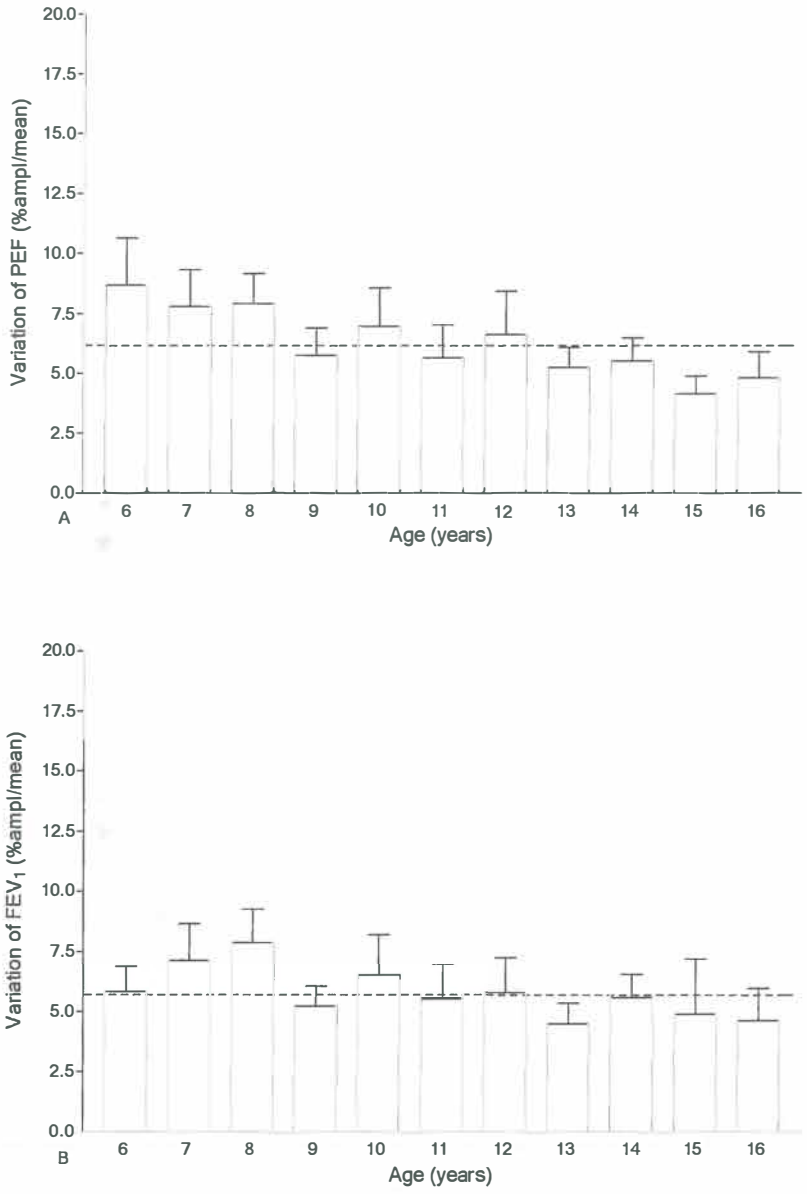

Figure 1AB. Variation in A) peak expiratory flow (PEF) and B) forced expiratory flow in one second (FEV_1). Data are presented as means (·····: overall mean). Vertical bars represent the 95% confidence interval. Variations are reasonably consistent between the different age groups, with a trend towards a lower variation of PEF in the older children. Single reference values for variation in PEF and in FEV_1 are possible.

Table 5. Characteristics of the 36 asthmatic children	
logPD_{20}-methacholine (μg)	1.98 (1.28-2.91)
FEV_1 (% pred)	99.1±12.6
FVC (% pred)	98.0±8.6
MEF_{50} (% pred)	79.7±21.7

Data are presented as median (inter-quartile range) or mean±SD, PD_{20}: provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (FEV_1); %pred: % predicted; FVC: forced vital capacity; MEF_{50}: mean expiratory flow when 50% of the FVC remains to be exhaled. Data from Brouwer et al.[14]

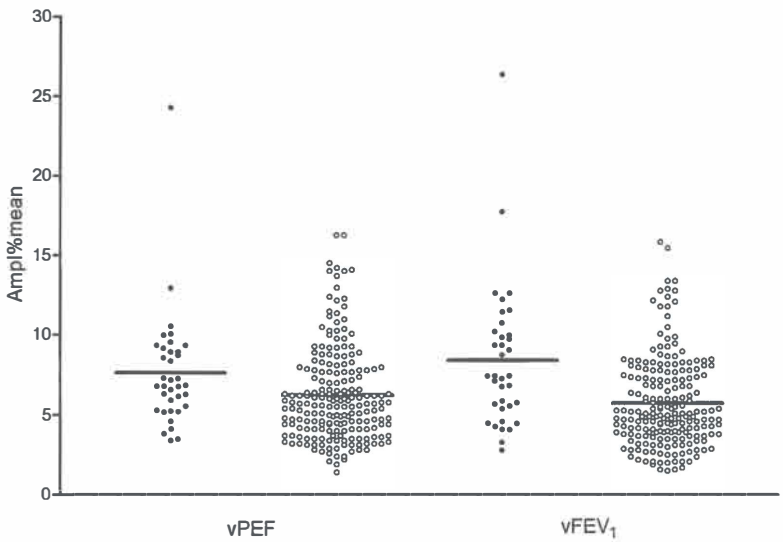

Figure 2. Variation of peak expiratory flow (PEF) and forced expiratory flow in one second (FEV_1) in asthmatic (●) and healthy children (○). Horizontal bars represent means. Although the means of both groups are significantly different for both PEF and FEV_1, there is considerable overlap between healthy children and well-controlled asthmatics. Data for asthmatic children from Brouwer et al.[14]

Discussion

The present study shows that, using home spirometry, healthy children exhibit substantially lower variation of lung function than previously described with mechanical PEF meters.[9] Since the previously described reference values were obtained using unreliable written PEF diaries[10,11], the present study used validated home spirometers with electronic data storage, generating more reliable reference values of variation of PEF and FEV_1.[12] There were no differences between male and female children. Although younger children showed significantly higher variation in PEF and FEV_1 than older children (table 2; fig. 1), this difference was considered too small and too variable to be of clinical relevance. Since PEF and FEV_1 variation were not dependent upon height or weight, and the influence of age was negligible, all data were pooled to give a single reference value of variation of lung function for all ages and sexes. Only two (<1%) subjects showed PEF or FEV_1 variation of >15%, and none of >20%. The day-to-day variability data showed similar results, also lower than those previously published[9], showing the stability of lung function measurements throughout the study. The present authors propose that the 95th percentiles from the present study, *i.e.* 12.3% for PEF variation and 11.8% for FEV_1 variation, be used as new reference values for diurnal variation of lung function in schoolchildren when using home spirometry under field conditions.

The reference values of PEF and FEV_1 variation in healthy schoolchildren were significantly lower than those recorded in a group of asthmatic schoolchildren with chronic persistent, but clinically stable, asthma (fig. 2). This suggests that home spirometry might be a useful diagnostic tool in the differentiation of asthmatic and nonasthmatic children. However, it should be emphasised that these results were obtained in selected groups of clearly healthy children on the one hand and children with a firm diagnosis of chronic persistent asthma who were diagnosed and followed- up in a specialised clinic on the other. Whether home spirometry will be a useful tool for ruling out or diagnosing asthma in children with nonspecific chronic respiratory symptoms remains to be evaluated in a separate study.

Some limitations of our study need to be discussed. Firstly, our study population was not a random population sample. For practical reasons, healthy schoolchildren were recruited by asking asthmatic children to approach their healthy peers to participate.

By applying strict exclusion criteria, which have proven to be useful in the selection of healthy subjects for obtaining lung function reference values[16], the present selection of healthy children should be representative of healthy nonasthmatic children. The application of these strict exclusion criteria precludes examination of the influence of passive smoke exposure on the present reference values. In studies using mechanical PEF meters and written diaries, diurnal PEF variation was up to 10% higher in children exposed to tobacco smoke.[28] Although this suggests that variation of PEF and FEV_1 recorded by home spirometry may be higher in healthy children of smoking parents than the values reported herein, this should be substantiated by further studies. Owing to the low prevalence of atopy in the present study cohort, it was not possible to examine its influence on PEF and FEV_1 variation in a meaningful way.

Secondly, the reference values were obtained using only one type of portable home spirometer. It is possible that the use of a different device may have rendered different results. It is unlikely, however, that this is clinically relevant. All home spirometers are designed for the same purpose, namely measuring lung function under field conditions, without the need for repeated calibration. All comply with ATS/ERS guidelines and have to be validated using computer-generated waveforms.[5] Although small differences between measurements obtained with home spirometers and hospital pneumotachographs have been found[23,29-31], manoeuvre reproducibility using home spirometry has been shown to be acceptable for a reliable calculation of variation in lung function.[13,23] In addition, although there is increasing evidence that younger children are able to exhale their complete vital capacity in <1s[32], the younger children in the present study showed that they could perform reliable FEV_1 measurements during the instruction sessions, and a maximum of only 2 measurements per child were excluded from analyses for this reason (data not shown). Furthermore, the children were warned by the device during the measurements when a blow was too short and then repeated the measurement correctly. Therefore, it is likely that the present reference values for PEF and FEV_1 variation are also applicable with other home spirometers. Finally, the technical quality of the forced expiratory manoeuvre was only checked during the instruction session at the start of the study and was not assessed at home. However, as mentioned above, a quality check is integrated into the home spirometer, warning the user, *via* an exclamation mark on the screen, if a manoeuvre is incorrectly performed. More importantly, other studies have shown that children

generate high-quality lung function values with home spirometry under field conditions after careful instruction.[13,15] This was also the case in the present study. Subjects recorded two usable recordings on >85% of days and showed no deterioration of PEF and FEV_1 variation over time. Furthermore, these reference values will be used in similar circumstances in clinical practice. Therefore, the present authors are confident that the reference values obtained for PEF and FEV_1 variation are of high quality and can be used in clinical practice and research.

To the present authors' knowledge, the present reference values are the first values published for variation in both PEF and FEV_1 using home spirometry with electronic data storage. Since FEV_1 is considered to reflect the patency of intrathoracic airways more reliably than PEF and is less effort dependent[2,5], FEV_1 may well be a more useful measure of lung function monitoring in children than PEF. Although monitoring lung function at home is advocated in guidelines on the long-term management of asthma, studies have consistently shown that such home monitoring of lung function and according modification of long-term treatment does not improve asthma control or outcome.[33-36] As a result, the present authors would not encourage the use of the current reference values in asthma self-management. The present authors believe, however, that the current study results support the hypothesis that home spirometry might be used as a diagnostic tool for childhood asthma in children with chronic wheeze, cough, or dyspnoea, when history, physical examination and office spirometry are insufficient to make or exclude the diagnosis reliably. This hypothesis will have to be tested in a study specifically designed to that end. The use of PEF diaries to distinguish asthmatic from nonasthmatic children has been largely abandoned as previous studies showed almost complete overlap in PEF variation between asthmatic[6,7] and healthy children, with a 95th percentile as high as 31% for PEF variation in healthy children.[9] It is now deemed highly likely that these reference values were spuriously high because they were obtained using unreliable written PEF diaries. If the present reference values for PEF and FEV_1 variation are compared to levels of such variation in well controlled asthmatic children using an electronic home spirometer as monitoring tool, there is much less overlap in variation of lung function between healthy children and children with asthma, even when the latter were using inhaled corticosteroids.[10,13,14] For example, in the previously published study of well-controlled asthmatic children using inhaled corticosteroids, 62% showed a PEF variation of >12.3% in any given week during a 3-month study period, using the same home spirometer[14], despite (near) normal lung

function (table 5). Given the fact that inhaled corticosteroids reduce PEF variation considerably[6,7], it is highly likely that even more symptomatic asthmatic children will show a variation of lung function above the present reference values when they are not using inhaled corticosteroids. Prospective studies, however, are needed to examine the diagnostic value of home spirometry for the identification of asthma in children in whom history and physical examination are insufficiently helpful in ruling asthma in or out as the cause of chronic respiratory symptoms.

In conclusion, the 95th percentiles of variation in peak expiratory flow and forced expiratory volume in one second in healthy schoolchildren, using home spirometers with electronic data storage, are 12.3% and 11.8%, respectively. This is considerably lower than previously reported reference values for peak expiratory flow variation obtained using mechanical meters and written diaries, and reduces the amount of overlap between healthy and asthmatic children. Further prospective studies are required to investigate whether or not home spirometry could be a useful diagnostic tool for childhood asthma.

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Chapter 6

Is home spirometry useful in diagnosing asthma in children with nonspecific respiratory symptoms?

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Abstract

Background

Variation of lung function is considered to be a hallmark of asthma. Although guidelines recommend measuring it as a diagnostic tool for asthma, the usefulness of this approach has not been studied in children.

Aim

To assess the usefulness of home spirometry in children with nonspecific lower respiratory tract symptoms, to diagnose or exclude asthma.

Methods

In school-aged children, referred by their general practitioner because of chronic respiratory symptoms of unknown origin, the diagnosis of asthma was made or excluded by a pediatric pulmonologist (gold standard), based on international guidelines and a standardized protocol. Additionally, children measured peak expiratory flow (PEF) and FEV_1 twice daily for 2 weeks on a home spirometer, from which diurnal variation was calculated. These results (index test) were not revealed to the pediatric pulmonologist. The value of home spirometry to diagnose asthma was calculated.

Results

61 children (27 boys) were included (mean age:10.4 yrs; range: 6-16 yrs). Between asthma and no asthma, the mean difference in PEF variation was 4.4% (95%CI:0.9 to 7.9;p=0.016) and in FEV_1 variation 4.5% (95%CI:1.6 to 7.4;p=0.003). Sensitivity and specificity, based on the 95^{th}-centile of the reference values for PEF and FEV_1 variation (12.3% and 11.8%, respectively) were 50% and 72% for PEF variation and 45% and 92% for FEV_1 variation. The likelihood ratio was 1.8 for PEF and 5.6 for FEV_1.

Conclusions

The contribution of home spirometry in the diagnostic process for asthma in schoolchildren with non-specific respiratory symptoms is limited.

Introduction

Asthma in children is a clinical diagnosis, and international guidelines recommend to use reversibility of bronchial obstruction measured by flow-volume curves to establish the diagnosis.[1,2] Spirometry is particularly indicated if symptoms are nonspecific and the diagnosis remains uncertain.[1,2] However, because variation of airway obstruction is a hallmark of asthma, most children with asthma will not exhibit reversibility at each assessment.[3] Therefore, the snap-shot lung function test lacks sensitivity.[2] Increased diurnal variation of lung function over a period of one to two weeks has been proposed as a diagnostic tool for asthma.[4] However, population studies using portable mechanical peak expiratory flow (PEF) meters, showed considerable overlap in PEF variation between healthy and asthmatic children.[5] As a consequence, the role of measuring diurnal PEF variation as a diagnostic tool for asthma in children has diminished.[6] Guidelines have been adapted accordingly,[1] although the GINA guideline still considers diurnal PEF variation of additional value for the diagnosis and classification of asthma.[2]

All original studies on the diagnostic usefulness of PEF variation used mechanical PEF meters and written diaries, which have proven to be unreliable.[7] Recently, we published reference values of PEF and forced expiratory flow in one second (FEV_1) variation using electronic home spirometry, showing limited overlap between healthy and treated, well controlled asthmatic children on inhaled corticosteroids.[8] From earlier studies, we know that PEF variation decreases significantly during the first two months of treatment with inhaled corticosteroids.[9] This suggests that the

difference in diurnal PEF and FEV_1 variation between not yet diagnosed –untreated– children with asthma and non-asthmatic children may be larger than previously thought, and that home spirometry could be a diagnostic tool for asthma when symptoms are nonspecific. To test this hypothesis, we studied the usefulness of home spirometry in diagnosing asthma in school-aged children referred for evaluation of nonspecific lower respiratory tract symptoms.

Patients and Methods

This study was set up to evaluate the diagnostic value of home spirometry in children with nonspecific respiratory symptoms, such as cough and breathlessness, in whom the general practitioner was uncertain about the diagnosis of asthma. Consecutive children, 6 to 16 years of age, referred to our hospital-based pediatric asthma clinic because of chronic respiratory symptoms of unknown origin were asked to participate in this study. The following children were excluded: children with a straightforward diagnosis of asthma based on classical respiratory symptoms, children referred because of poorly controlled asthma and children with reported use of systemic corticosteroids or long-acting beta-2-agonists within four weeks prior to the referral date. This study was approved by the hospital ethics review board, a certified subsidiary of the Dutch central committee on research involving human subjects.

Based on earlier studies, a period of 2 weeks of home spirometry measurements was chosen because this is sufficient to show increased lung function variation in children with untreated asthma,[4] and adherence to home spirometry is high.[10,11] A sample size calculation was performed as follows: for PEF and FEV_1 variation, we anticipated a standard deviation of 3.5%, equal for both groups.[11] In order to be able to detect a minimal difference of 4% in PEF and FEV_1 variation between an asthma and a no asthma group –with an α of 0.05 and a power of 90%–, 18 data pairs were needed. We estimated that in approximately 60% of the referred patients the diagnosis of asthma would be made; therefore, including 45 patients would suffice. In order to allow non-compliance or data errors, we aimed to include 60 patients.

After obtaining written informed consent from patients and parents, children were included and if applicable, inhaled corticosteroids (ICS) were withdrawn. Fourteen days later, at a first visit to our asthma clinic, a semi-structured medical history was taken and physical examination was performed by a pediatric pulmonologist. The fraction of exhaled nitric oxide (FeNO) was measured using a portable NO-meter (NIOX MINO, Aerocrine, Solna, Sweden)[12] according to international recommendations,[13] and expressed in parts per billion (ppb). Subsequently, patients performed flow-volume loops before and 20 minutes after inhalation of 800µg salbutamol. All lung function measurements were performed on a Jaeger Masterlab pneumotachograph (Erich Jaeger, Würzburg, Germany), following ATS/ERS guidelines,[14] and short-acting bronchodilators were withdrawn for 8 hours prior to each lung function session. At the second study visit 2 weeks later, history, physical examination and FeNO measurements were repeated, and bronchial responsiveness was assessed by methacholine provocation using the dosimeter method.[15,16] Results were expressed as the provocative dose of methacholine causing a 20% fall in FEV_1 (PD_{20}). During the 2-week study period, only short acting bronchodilators when needed were allowed, and children were instructed to return to our clinic immediately if symptoms remained uncontrolled.

During the 2-week study period between the two study visits, children measured PEF and FEV_1 twice daily on a home spirometer (index test). These results were not revealed to the pediatric pulmonologist at any time during the study. During the first visit, patients were instructed carefully how to use the electronic portable spirometer (Koko Peak Pro, Ferraris, Louisville, Colorado, USA).[14,17]

This home spirometer has been validated both in vitro by using a precision waveform generator (Pulmonary Waveform System; MH Custom Design and Mfg, Midval, UT, USA) demonstrating its agreement with performance standards as recommended by international guidelines,[14] and in vivo in schoolchildren with asthma.[18] Patients were instructed to perform three forced expiratory flow manoeuvres twice daily between 6AM and 10AM and between 6PM and 10PM throughout the whole study period of 2 weeks. The device automatically stored the highest of the three correctly performed PEFs on a microchip, along with the accompanying FEV_1. All instructions were given by the same experienced technician, encouraging the children to obtain optimal lung function values. At least one parent attended the instruction session. Patients were instructed to achieve PEF as rapidly

as possible and to continue the forced expiratory manoeuvre for at least 2 seconds. An integrated quality check warned the user by an exclamation mark when a cough was detected, the blow was not long enough, or there was a slow start. After careful inspection following a predefined algorithm,[19] recordings due to technical errors and unexplained outliers were excluded. During analyses, measurements were only accepted if forced vital capacity exceeded FEV_1 and recordings were performed within the given time frame.

Adherence to home spirometry was calculated by comparing the number of recordings expected over 2 weeks with the number of recordings actually obtained. The PEF was expressed as percentage of the personal best value (%PB) and the FEV_1 as percentage of the predicted value (%pred).[20] Variation of PEF (and of FEV_1) was expressed as the amplitude (maximum-minimum) as a percentage of the day's mean (ampl%mean).[21]

At the second visit and after reviewing history, physical examination and lung function data, but without the home spirometry results (index test), a single experienced pediatric pulmonologist made or excluded the diagnosis of asthma in each patient (gold standard). When asthma was excluded the differential diagnosis was evaluated and further appropriate testing was performed – if necessary – until the diagnosis was reached.

The gold standard (asthma diagnosis by the pediatric pulmonologist) and the index test (PEF or FEV_1 variation by home spirometry) were compared, and test characteristics were calculated by using the 95^{th}-centile for PEF and FEV_1 variation in healthy schoolchildren, 12.3% and 11.8% respectively, as the cut-off between normal and increased PEF or FEV_1 variation.[8] Receiver operating characteristic (ROC) curves for PEF and FEV_1 variation were produced to assess the diagnostic performance of the index test. Data were analyzed using PRISM™ (GraphPad Software, San Diego, California, USA) for Windows™ version 3.00.

Results

Sixty-one children (27 boys) were included in this study, with a mean age of 10.4 years (range: 6-16 years). At inclusion, children had experienced nonspecific symptoms of recurrent wheeze or cough and breathlessness for at least three months, reported as partly relieved by bronchodilators. All children were able to perform pulmonary function measurements reproducibly. All children completed the study.

In 21 children (34%) asthma was diagnosed (asthma group). The remaining 40 children (64%) comprised the no asthma group and were diagnosed as follows: 13 children (33%) (allergic) rhinitis, treated successfully with nasal corticosteroids, 13 (33%) dysfunctional breathing, defined as chronic or recurrent changes in breathing pattern, causing respiratory and non-respiratory complaints,[22] which was confirmed and treated successfully by a physiotherapist, eight (20%) recurrent upper

Table 1. Distribution of patient characteristics between the asthma and no asthma group.

Diagnosis		No asthma (n=40)	Asthma (n=21)	p-value
Mean age (yrs)		10.5 ± 2.5	10.2 ± 2.7	0.690
Sex: (%male)		17 (43%)	10 (48%)	0.702
Family history of asthma(1st degree)		23 (58%)	16 (76%)	0.149
Symptoms:	Wheeze	11 (28%)	18 (86%)	<0.0001
	Cough	22 (55%)	15 (71%)	0.212
	Breathlessness	40 (100%)	21 (100%)	1.000
Smoking:	Parent(s)	12 (30%)	5 (24%)	0.608
	Patient	0 (0%)	1 (5%)	0.164
Sensitization:	No sensitization	22 (55%)	1 (5%)	<0.0001
	Only aero allergens	15 (37%)	17 (80%)	0.001
	Only food allergens	1 (3%)	1 (5%)	0.637
	Both	2 (5%)	2 (10%)	0.498
Medication:	No inhaled medication	7 (17%)	0 (0%)	0.042
	SABA* only	12 (30%)	6 (29%)	0.907
	ICS†	21 (53%)	15 (72%)	0.213
	Other asthma drugs	-	-	-

*short-acting beta-2-agonists; †inhaled corticosteroids.

respiratory tract infections, two (5%) serologically proven pertussis, three (7%) chronic persistent cough. In addition, there was one patient (3%), who, after further diagnostic work-up including body plethysmography and diffusion capacity measurements, appeared to have a restrictive lung function deficit, for which the underlying cause could not be determined. Asthma was excluded in this patient by the absence of wheeze, even while symptomatic, absence of bronchodilator and methacholine responsiveness, and normal FeNO values. Patient characteristics in the two groups are shown in table 1, and lung function results in table 2.

Table 2. Lung function characteristics of the 61 participating children showing statistically significant differences.

Diagnosis	No asthma (n= 40)	Asthma (n=21)	95%CI; p-value
1st visit FEV_1 (% pred) *	101.1 ± 11.3	86.4 ± 15.2	7.8 – 21.8; <0.0001
Increase in FEV_1 (% pred) after 800 µg salbutamol	3.5 ± 4.1	11.7 ± 6.0	5.5 – 10.9; <0.0001
1st visit FVC (% pred) †	100.1 ± 11.5	91.8 ± 13.8	1.7 – 15.1; 0.0153
1st visit FEV_1/FVC (%pred)	101.3 ± 6.5	94.0 ± 11.1	2.4 – 11.5; 0.0035
1st visit MEF_{50} (% pred) ‡	83.2 ± 16.5	62.3 ± 20.4	11.1 – 30.7; <0.0001
1st visit FeNO (ppb) §	28.5 ± 26.6	72.8 ± 39.1	26.6 – 62.0; <0.0001
2nd visit FEV_1 (% pred)	101.0 ± 11.5	85.4 ± 19.5	4.2 – 15.6; 0.0005
2nd visit FeNO (ppb)	32.2 ± 27.9	67.1 ± 41.5	15.5 – 54.2; 0.0007
logPD_{20}-methacholine (µg) ‖	3.15 [2.71 – 3.15]	1.83 [1.61 – 2.31]	0.8 – 1.3; <0.0001
Home Spirometry			
PEF (%PB) Σ	84.0 ± 8.3	76.9 ± 13.9	1.1 – 13.0; 0.0203
FEV_1 (%pred)	89.3 ± 13.5	75.5 ± 18.5	5.1 – 22.5; 0.0024

Values are presented as mean ± SD, or as median and inter-quartile range for PD_{20}. *forced expiratory volume in one second expressed as percentage of predicted value; †forced vital capacity; ‡maximal expiratory flow at 50% of expired volume; §fraction of exhaled nitric oxide expressed in parts per billion; ‖provocative dose of methacholine causing a 20% fall in FEV_1; Σpeak expiratory flow expressed as percentage of the personal best value.

Home spirometry data from two patients (one with asthma and one with no asthma) were lost due to battery failure of the device. There were no other technical errors. For the remaining 59 patients, mean adherence to home spirometry during the 2-week study period was 93% (SD 8.8%), and this was comparable in the asthma and no asthma group (mean difference 0.1%, 95%CI -4.9% to 4.7%; p=0.98). Figure 1 shows the distributions of PEF and FEV_1 variation in the asthma and the no asthma groups. The mean differences in PEF variation and FEV_1 variation between the two groups were 4.4% (95%CI 0.9 to 7.9; p=0.016) and 4.5% (95%CI 1.6 to 7.4; p=0.003), respectively. Test characteristics of increased PEF and FEV_1 variation for the diagnosis of asthma, using the 95^{th}-centile of the reference values for PEF and FEV_1 variation (12.3% and 11.8%, respectively) as cut-off[8], are shown in table 3.

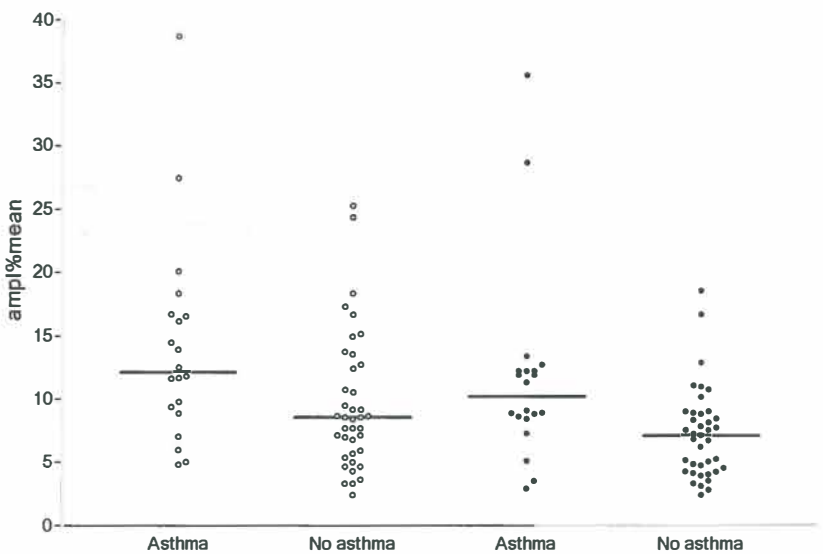

Figure 1. Distributions of PEF and FEV_1 variation in the asthma and the no asthma group showing complete overlap for both home spirometry indices between the two groups. ○: PEF variation. ●: FEV_1 variation. Lines represent median values.

Table 3. Test characteristics calculated when the 95th-centile of the reference values for PEF and FEV_1 are used.

	PEF* variation ≥ 12.3%	FEV_1† variation ≤ 11.8%
Sensitivity (95%CI)	0.50 (0.30 to 0.70)	0.45 (0.25 to 0.67)
Specificity (95%CI)	0.72 (0.56 to 0.84)	0.92 (0.80 to 0.97)
Positive predictive value (95%CI)	0.48 (0.28 to 0.68)	0.75 (0.47 to 0.91)
Negative predictive value (95%CI)	0.74 (0.58 to 0.85)	0.77 (0.63 to 0.86)
Likelihood ratio (95%CI)	1.77 (0.91 to 3.45)	5.85 (1.78 to 19.24)

*peak expiratory flow; †forced expiratory volume in one second.

Receiver-operating characteristic (ROC) curves for PEF and FEV_1 variation are shown in figures 2A and 2B, respectively. The area under the curve (AUC) is 0.69 for PEF variation and 0.77 for FEV_1 variation.

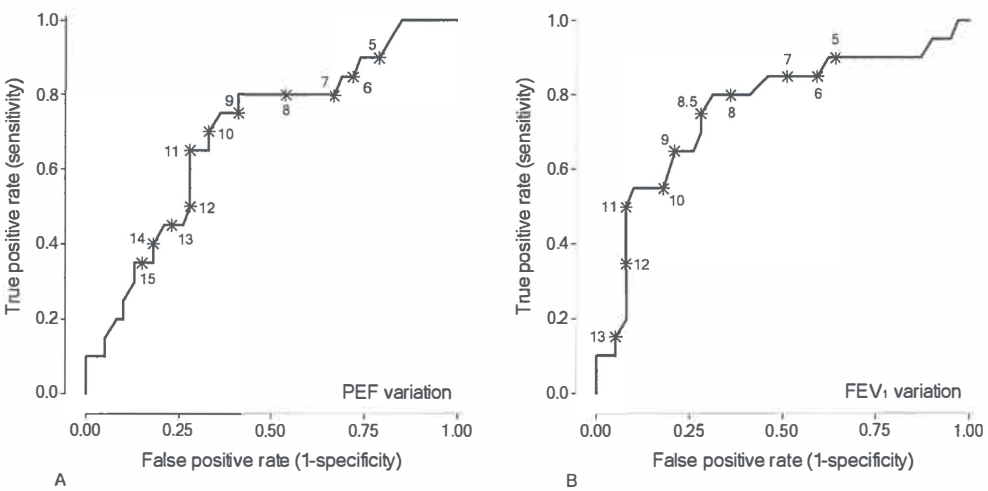

Figure 2. Receiver operating characteristics curves for A) PEF variation and B) FEV_1 variation showing the poor diagnostic performance of both home spirometry indices. Area under the curve (AUC) for PEF variation: 0.69; AUC for FEV_1 variation: 0.77. Numbers in the graphs represent the associated cut-off values for PEF and FEV_1 variation, respectively (ampl%mean).

Discussion

This study shows that the diagnostic value of home spirometry in making or excluding the diagnosis of asthma in schoolchildren with nonspecific respiratory symptoms, such as cough and breathlessness, is limited. Although mean variation of PEF and FEV_1 using home spirometry were significantly lower in the no asthma group than in the asthma group, the difference was small, and the distributions of PEF and FEV_1 variation showed complete overlap between the two groups (figure 1). Home spirometry contributed marginally to the likelihood of asthma, with likelihood ratios of 1.77 and 5.85 for PEF and FEV_1 variation, respectively. The receiver operating characteristic curves (figure 2) illustrate the poor diagnostic performance of PEF and FEV_1 variation using home spirometry in schoolchildren with chronic nonspecific respiratory symptoms.

A well-recognized difficulty in the diagnosis of asthma in children is the lack of one reliable diagnostic test, in particular when symptoms are nonspecific. Asthma is a clinical diagnosis based on multiple key indicators increasing the probability of the presence of the disease.[1,2] Wheezing is considered a key symptom in asthma, but because patients and parents vary considerably in their interpretation of 'wheeze' (which may include any kind of noisy or difficult breathing),[23,24] the presence of expiratory wheeze, as a sign for the presence of airflow obstruction, should be confirmed by a health care professional, either by physical examination or by lung function testing.[2,24,25] This is corroborated by the results of our study, in which a history of wheezing, although more common in the asthma group, was also present in a quarter of the patients in the no asthma group. (table 1)

Because we aimed to assess the diagnostic value of home spirometry in children with nonspecific respiratory symptoms specifically, we excluded children with a straightforward diagnosis of asthma based on classical respiratory symptoms. The main reason for this approach was that home spirometry would not have to be used in such patients to confirm the diagnosis of asthma. In clinical practice, an assessment of lung function variation is primarily used to help making or rejecting the diagnosis of asthma in patients in whom history and physical examination alone are insufficient to make or reject the diagnosis. This study was designed to test the usefulness of home spirometry in exactly that clinical population. Children referred

because of poorly controlled asthma were excluded because of the increased exacerbation risk after the withdrawal of inhaled corticosteroids.

Guidelines recommend additional lung function tests to establish the diagnosis,[1] or increase its likelihood.[2] In this study, we used FeNO, lung function, bronchodilator response and bronchial hyperresponsiveness to help making or rejecting the diagnosis of asthma in schoolchildren experiencing nonspecific respiratory symptoms. By combining the results of these tests and the suspected presence of asthma based on the semi-structured medical history and the physical examination, we assured that the diagnosis of asthma was made reliably and according to international guidelines.[1,2] As a result of this study design, the diagnostic properties of each of the separate tests which were used to make the diagnosis can not be reported. Home spirometry did not emerge as a reliable diagnostic test for asthma in children with nonspecific respiratory symptoms.

The likelihood ratio of a test represents the change in disease probability after performing the test.[26] With a pre-test probability of asthma of 34% in our study population, the likelihood ratio of 1.77 for PEF variation leads to a post-test disease probability of approximately 44%. Such a small increase in disease likelihood underscores the poor diagnostic value of PEF variation in the diagnosis of asthma.[26,27] The likelihood ratio of 5.85 for FEV_1 variation increases the post-test disease probability considerably to approximately 73%, mainly because the specificity of increased FEV_1 variation is larger than that of PEF variation (table 3). However, the sensitivity of increased FEV_1 variation was poor, identifying less than half of the asthmatics in the present study (table 3, figure 1). The receiver operating characteristic curve of FEV_1 variation (figure 2B) shows that the false positive rate rises quickly when lower cut-off values of FEV_1 variation are used to increase sensitivity. In addition, the large degree of overlap in FEV_1 variation between the asthma and no asthma group (figure 1) limits its usefulness in individual patient care. Therefore, despite the reasonable likelihood ratio, the applicability of FEV_1 variation as a diagnostic test for asthma in children with nonspecific respiratory symptoms is limited.

Some limitations of the present study need to be discussed. Firstly, the quality of data obtained by home spirometry must be considered. Previous studies have consistently shown that home spirometry provides reproducible and technically

reliably results,[27-29] although they are slightly lower than those obtained by hospital spirometry.[18]

Secondly, like earlier diagnostic studies in childhood asthma,[4,30] this study was powered to detect a minimal difference between two groups, but not to establish agreement between two tests (gold standard and index test). Although adequately sized groups were formed and the expected minimal difference of 4% was found, establishing agreement between two clinical tests would have taken at least 50 data pairs.[31] With only 34% of the referred children receiving a diagnosis of asthma, a total of 150 inclusions would have been necessary. Nevertheless, the complete overlap in distributions of PEF and FEV_1 variation between the asthma and no asthma group (figure 1) makes it unlikely that increasing the sample size of our study would have changed its results in a clinically relevant way.

In conclusion, this study shows that the usefulness of home spirometry in the diagnostic process of asthma in children with nonspecific respiratory symptoms is limited. Even if obtained by electronic home spirometry, PEF and FEV_1 variation should not be used as a diagnostic tool for asthma in children with nonspecific chronic respiratory symptoms.

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Chapter 7

General discussion

General discussion

The general aim of this thesis was to explore the usefulness of electronic home spirometry measuring lung function variation in monitoring disease severity in childhood asthma and in making the diagnosis of asthma in children. The foundation of this thesis was provided by the study by Kamps et al, showing the unreliability of written peak expiratory flow (PEF) diaries in childhood asthma (figure 1).[1,2] Because the disadvantage of unreliable written paper PEF diaries does not apply to electronic home spirometers, it is assumed that these home spirometers provide a suitable

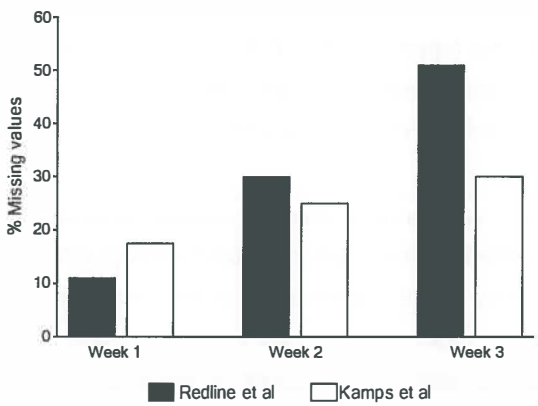

Figure 1. Summary of results of two studies examining adherence to PEF diary keeping in children with asthma. In both studies, children were unaware that their PEF diary adherence was being monitored. Bars represent the percentage of values missing from the electronic diary but recorded in the written diary during the first three weeks of PEF monitoring. Black bars, black inner city children,[37] white bars, white children from affluent families.[1] Reproduced with permission from Kamps et al.[2]

alternative for monitoring the severity of asthma in children.[3,4] Although intuitively appealing, the usefulness of home spirometry in the follow-up of childhood asthma is supported by little evidence.

Earlier studies, using written PEF diaries, showed a weak correlation between lung function variation and other parameters of asthma severity.[5-7] However, the correlation between asthma severity and home measured peak flow variation assessed by home spirometry was unknown. The studies in this thesis show that the usefulness of home spirometry in childhood asthma, whether for monitoring disease severity or for making the diagnosis of asthma, is limited *(chapters 3, 4 and 6).* Based on these results, we recommend that international guidelines be adapted. Presently, the use of home spirometry to monitor childhood asthma can not be recommended. Consequently, alternative methods should be studied to monitor the day-to-day variation of the disease.

Validation of the home spirometer and quality of the measurements

All studies presented in this thesis used the same kind of electronic portable spirometer (Koko Peak Pro, Ferraris, Louisville, Colorado, USA; figure 2). This home spirometer has been validated using a precision waveform generator (Pulmonary Waveform System; MH Custom Design and Mfg, Midval, UT, USA) demonstrating its agreement with performance standards as recommended by international guidelines.[8] The device is relatively low-cost (approximately € 40) and easy to handle for both patient and clinician. It is accompanied by simple software and can be linked directly to a computer by an infra-red connection in a cradle (figure 2).

The device measures both PEF and FEV_1, without the need for regular calibrations. We found that the home spirometer yielded reproducible and quality acceptable PEF and FEV_1 measurements. Although they were significantly lower than results obtained by hospital spirometry, and they can not be used interchangeably with office-based spirometry measurements, PEF and FEV_1 measured by home spirometry are suitable to assess diurnal peak flow and FEV_1 variation, and to assess actual peak flow and FEV_1 values prospectively *(chapter 2).* Therefore, the electronic home

Figure 2. Koko peak pro in a cradle, the docking station, with an infra-red connection to download and process data.

spirometer is a useful device for home recording of lung function under field conditions.

Adherence to home spirometry

The high adherence observed in all studies in this thesis suggests that children are more willing to record lung function electronically on a home spirometer than to record values on a mechanical peak flow meter.[1] This difference is possibly caused by the novelty and attractiveness of the electronic device, but in the context of the studies it may also be due to the fact that the children and their parents were aware that missing values would be noticed. Although overall adherence in the studies was very high, it is still considerably lower than the adherence reported in adults using an electronic peak flow device in a similar research setting.[9] Whilst the adherence to home spirometry in adults decreased slowly from 96% in the first eight weeks to 89% after a total of 72 weeks,[9] the adherence of children in our studies decreased more rapidly from approximately 95% in the first two weeks to nearly 90% after only 13 weeks *(chapters 3 and 6).* In addition, in the healthy school children *(chapter 5)* the adherence during 2 weeks of home spirometry was only 86%, possibly due to the fact that they and their parents were not used to examine their health status daily.

Furthermore, in the children with asthma who were instructed to measure lung function also at time of symptoms *(chapter 4)*, after 8 weeks the median adherence dropped below 85%. This suggests that children are initially as adherent to home spirometry as adults, but they lose their motivation more rapidly. Apparently, the novelty and attractiveness of the home spirometer wear off rapidly for children. This undermines the usefulness of long-term home spirometry in children. All children were surprisingly loyal in keeping the simple symptom diaries during the relevant studies *(chapters 3 and 4).* The straightforwardness and the single item per sequence to address may have enhanced the adherence to the symptom diary.[10] However, because the reliability of the symptom diaries could not be verified, its results should be interpreted cautiously.[11]

Technical errors

Approximately 1% of the registrations from the home spirometer were useless as a result of technical errors including tampering with the device (figure 3), use by family members and friends, and battery failure. Due to the natural curiosity of children, such technical errors are – to some degree – unavoidable,[12] and have shown to be present in similar proportions in various other devices.[13,14] Although such technical errors are easily recognizable, recorded data must be thoroughly and manually scrutinised before they can be interpreted, thus limiting the appealing 'plug and play' feature of electronic home spirometers.

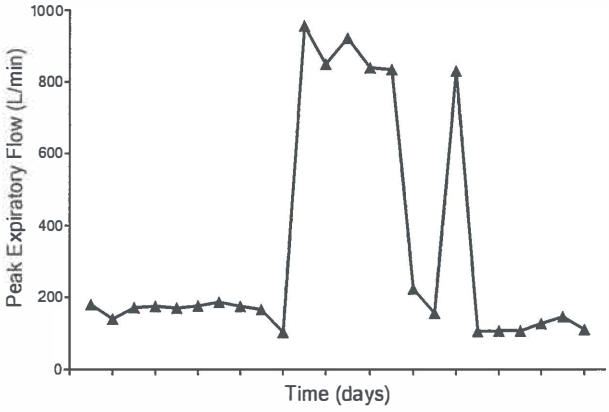

Figure 3. Tampering with the device by pushing the metal plate behind the mouth peace manually and producing spuriously high peak flows.

Technical quality

One potential limitation of all studies performed as part of this thesis, is the technical quality of lung function measurements in home spirometry. At home, measurements are not performed under supervision of a skilled lung function technician, who can encourage a child to obtain optimal recordings by using computer incentives or animations *(chapters 3,4,5 and 6).* Furthermore, the device used in our studies does not provide visual feedback of correct performance, and does not record flow-volume loops for visual inspection and quality control. Previous studies have shown, however, that the technical quality of home spirometry recordings in children is usually acceptable.[13] Additionally, the home spirometer used in this thesis had an integrated quality check, warning the user, by an exclamation mark on the screen, when a cough was detected, the blow was not long enough, or the start of the expiratory manoeuvre was too slow.[15,16] In the event of such a warning, children were instructed to repeat the measurements immediately and the device would erase the incorrectly obtained values from the microchip. During analyses, outliers, remaining measurements with an attached warning, and measurements with an FEV_1 not exceeding the accompanying FVC, were deleted to optimize the quality of the data *(chapters 3,4,5 and 6).* We are therefore confident that the data obtained by home spirometry in this thesis were technically acceptable and valid.

Another potential limitation concerning the reliability of the measurements is the influence of bronchodilators on the PEF and FEV_1 measurements at home.[17,18] However, given the low use of rescue bronchodilators in the studies presented, and the recording of the timing of their use, it is highly unlikely that the findings were influenced by bronchodilators used during the day and before measurements.[18]

When compared to hospital pneumotachography, we found an acceptable manoeuvre reproducibility showing the consistency of measurements on the device *(chapter 2)*. However, peak flow, and FEV_1 to a smaller extent, was significantly lower on the home spirometer than values obtained from hospital pneumotachography (table 1), excluding home spirometry as a valid proxy for clinical spirometry *(chapter 2)*. We concluded that home spirometry generates reproducible and quality acceptable PEF and FEV_1 measurements. Although they are lower than those obtained by hospital spirometry and these results can not be used

Table 1. Mean spirometry data for the whole study population.*(chapter 2)*

	Mean ± SD	95% CI
Home spirometer		
Mean PEF (L/min)	278 ± 78	256–300
Mean FEV_1 (L)	2.35 ± 0.75	2.14–2.56
Pneumotachograph		
Mean PEF (L/min)	300 ± 91	274–326
Mean FEV_1 (L)	2.41 ± 0.79	2.19–2.63
Between devices		
Mean difference in PEF (L/min)	22 ± 29	14–30
Mean difference in FEV_1 (L)	0.06 ± 0.13	0.02–0.10

PEF: peak expiratory flow; FEV_1: forced expiratory volume in the first second; SD: standard deviation.

interchangeably, home spirometry appears to be suitable to assess peak flow and FEV_1, and their diurnal variation at home *(chapter 2)*.

Home spirometry and monitoring disease severity

This thesis shows that the relationship of lung function variation (both PEF and FEV_1), as assessed by home spirometry, to other parameters of asthma severity, such as airway hyperresponsiveness, bronchodilator response, asthma symptom scores and quality of life, is highly variable between patients and is therefore too inconsistent to be clinically useful *(chapter 3)*. We also showed that the poor concordance of PEF variation, assessed by using mechanical PEF meters and written PEF diaries,[5,6] to other parameters of asthma severity is not overcome by using electronic home spirometers. Furthermore, this thesis found that the degree of airway narrowing at times of respiratory symptoms, prompting the use of reliever therapy, is highly variable between children with asthma (figure 4; *chapter 4)*.

Due to this highly variable relationship between symptoms, FEV_1 and PEF between patients, it is unclear what change in which parameter the patient is expected to respond to when monitoring and self-managing the disease at home, and whether this influences clinically relevant outcomes. Although the limitations of PEF

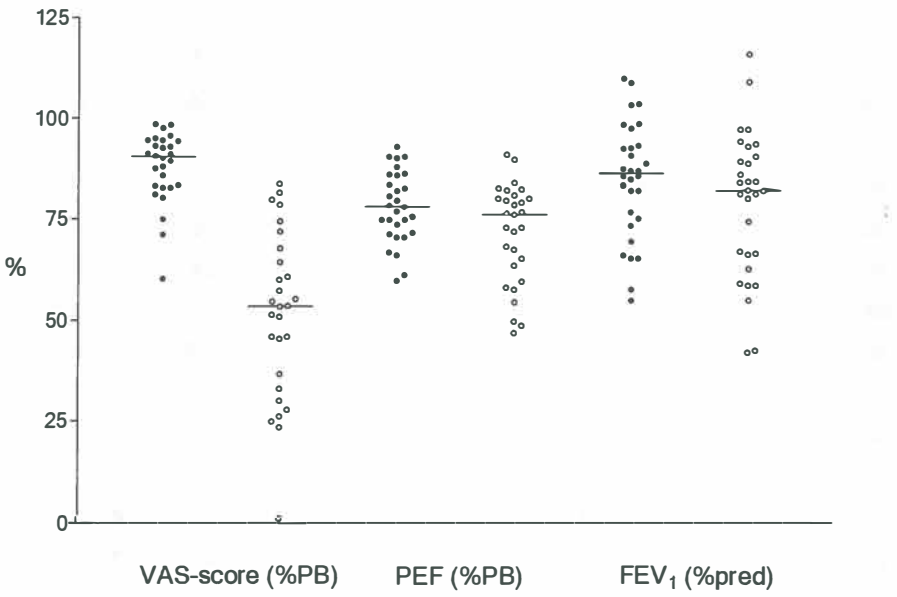

Figure 4. Home spirometry and symptom scores: Symptom free days compared to 'at times of symptoms'. ●: symptom free days (SFD); ○: at times of symptoms (ATOS). VAS: visual analogue scale expressed as percentage of personal best value; PEF: peak expiratory flow expressed as percentage of personal best value; FEV_1: forced expiratory volume in one second expressed as percentage of predicted value.*(chapter 4)*

monitoring are well recognized,[19,20] only one RCT on the usefulness of home spirometry was conducted to date. This study found no beneficial contribution of home spirometry to important self-management decisions, such as taking reliever medication, and did not improve asthma control or outcome.[21] In addition, this thesis provides evidence of poor concordance of home spirometry with asthma severity and acute symptoms, and it shows that these relationships also vary considerably between patients. Taken together, these results limit the usefulness of home spirometry in the monitoring and management of childhood asthma *(chapters 3 and 4)*.

Peak expiratory flow versus FEV_1

It is generally assumed that home or hospital PEF measurements are of limited use because they are dependent on the patient's effort, and they mainly reflect large airway calibre instead of the increased small airways resistance characteristic of asthma.[22,23] FEV_1 is less dependent than PEF on the patient's effort and is a better estimate of smaller airways obstruction.[8,23-25] Theoretically, therefore, home monitoring of FEV_1 could provide a more reliable assessment of variation of airways obstruction than PEF monitoring. Although home spirometry provides reproducible and quality acceptable PEF and FEV_1 measurements *(chapter 2)*, we found an unexpected poor concordance of changes in PEF with changes in FEV_1 *(chapter 3)*. Similarly, falls in PEF below commonly used cut-off values for stepping up asthma therapy in self-management plans were accompanied by a wide range of drops in FEV_1 and vice versa *(chapter 3)*.

It is quite clear that monitoring both parameters simultaneously in a self-management plan would cause uncertainty, because it is unclear which change the patient is expected to respond to. With discordance between PEF and FEV_1 changes occurring in approximately 33% of children with mild-to-moderate asthma, self-management would become unacceptably complicated in many patients with asthma *(chapter 3)*. This poor concordance may be caused by the superiority of FEV_1 to reflect airways obstruction.[8,23-25] However, the relationship of FEV_1 variation to other parameters of asthma severity was as variable as that of PEF variation *(chapter 3)*. Furthermore, we found no difference between PEF and the potentially more sensitive FEV_1 decrease at time of respiratory symptoms *(chapter 4)*. These data are in accordance with the results of the RCT using home spirometry in self-management, which found no increased sensitivity in monitoring FEV_1 as a secondary outcome, when compared to PEF.[21] These results, therefore, suggest that home spirometry FEV_1 measurements also have limited value for home monitoring purposes. Apparently, the theoretical advantage of home FEV_1 measurements does not come true in practice.

Monitoring acute symptoms

In the last edition of international asthma guidelines, assessment of asthma control has become the cornerstone of asthma monitoring and follow-up [3,4,26] (table 2). This assessment of asthma control is largely based on the patient's perception of acute symptoms and the need for reliever therapy.[3,4] It is suggested that the symptoms

that children experience represent a sum of different asthma-related sensations and perceptions over time, whilst lung function represents a snapshot impression of asthma status at a given point in time.[21] Since many children with asthma, as well as their parents, are poor perceivers of airway obstruction,[22,27,28] relying only on the patient's recognition of asthmatic symptoms may lead to both overtreatment or undertreatment.[22,28,29] This is why monitoring of lung function is advocated in asthma guidelines.[3,4]

This thesis, however, found that patients vary considerably in the relationships between symptom scores, PEF and FEV_1 *(chapter 3 and 4).* In addition, the degree of airway narrowing at times of respiratory symptoms, prompting the use of reliever therapy, was also highly variable between children with asthma *(chapter 4).* This finding hampers the applicability of the approach of variable inhaled corticosteroid and long-acting beta-2-agonist dosing in children.[30] Overall, although PEF and FEV_1 were significantly lower at time of symptoms than at moments when the patient was asymptomatic, this change was both highly variable between patients and relatively small (6.6% for personal best PEF, and 6.0% for %predicted for FEV_1); the change in symptom scores between times of symptoms and asymptomatic days was much larger (36.2% for personal best) *(chapter 4).* In addition, the distributions of PEF and FEV_1 in individual patients showed complete overlap between symptom-free days

Table 2. Levels of asthma controle. From the GINA guidelines.[4]

Characteristic	Controlled (all of the following	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakenings	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV_1)	normal	< 80% predicted or personal best (if known)	
Exacerbations	None	One or more/year	One in any week*

*By definition, an exacerbation in any week makes that an uncontrolled asthma week.

and at time of symptoms (figure 4)*(chapter 4)*. Because no gold standard exists to determine whether the symptom scores or the home spirometry results adequately reflect asthma status, only RCTs using symptoms scores versus home spirometry can answer the question which parameter should be used. A recent systematic review on this subject, including only one RCT using home spirometry in children,[21] showed that monitoring symptom scores is superior to PEF monitoring in childhood asthma.[31] However, the children in our study, as a group, showed more symptoms than could be explained by their degree of airway narrowing. Apparently, children with asthma commonly report dyspnea or wheeze without objective evidence of airway obstruction *(chapter 4)*. In conclusion, home PEF or FEV_1 monitoring offers no advantage over symptom monitoring in the follow-up of asthma in children, therefore home PEF or FEV_1 monitoring should not be advocated in asthma guidelines.

Different association patterns

In this thesis, we describe four different association patterns between symptom scores and lung function variation over time in children with asthma: reasonable concordance, chaos, poor perception or excessive symptoms (figure 5; *chapters 3 and 4)*. These association patterns are based on visual inspection and classification of home spirometry and symptom diary data, and arose from the observation that although PEF variation reflected the variability of the asthma symptom scores in some patients, in most cases there appeared to be no relationship at all. These observations concur with earlier studies using mechanical PEF meters.[32] Identifying poor perceivers and patients with excessive symptoms would be clinically useful, and thus may help to predict functional morbidity of asthma in children.[24] However, to be clinically useful, such a classification system of patients should be straightforward, and should be repeatable between observers.

We found a fair inter-rater agreement of this preliminary classification system *(chapter 4)*. Further studies are needed to develop a more robust and repeatable classification system of poor perception and excessive symptoms, with or without the use of home spirometry. Ideally, such a system should provide a clear and consistent signal to patients how they need to respond. Given the high variability between patients in symptom scores, PEF, and FEV_1, and their agreement over time, the development of such a system is expected to be fraught with difficulties. Meanwhile, clinicians should be aware that the relationship between

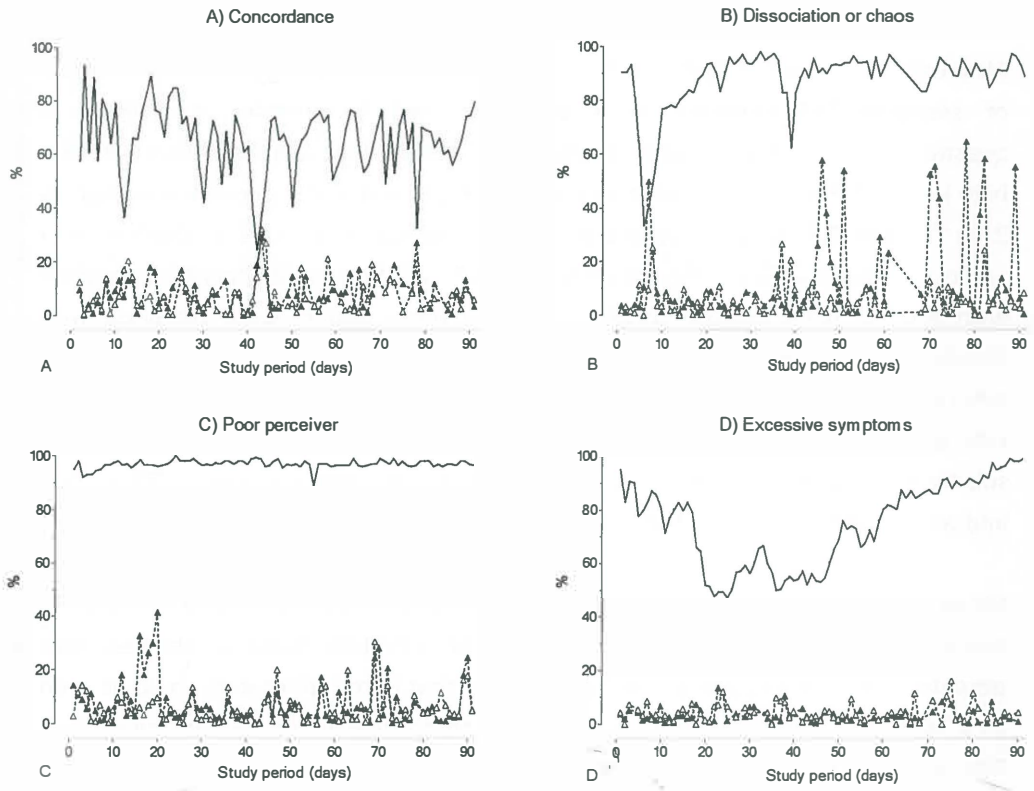

Figure 5. Samples of individual monitoring data showing four different patterns of relationships between asthma severity score, forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) variation. a): concordance of patients ; b): dissociation or chaos; c): poor perceiver; and d): excessive symptoms categories.*(chapter 3)* ——: asthma severity score (percentage of personal best); Δ: PEF variation (expressed as size of day's range as a percentage of the day's mean (ampl/mean); ▲: FEV_1 variation (ampl/mean).*(chapter 3)*

symptoms of asthma and lung function variation over time is highly variable between patients, and chaotic and erratic in many. Again, this limits the usefulness of home spirometry as a monitoring tool in childhood asthma.

The role of home spirometry in diagnosing asthma

Although it is still advocated in asthma guidelines for monitoring purposes,[4] the role of assessing PEF variation as a diagnostic tool for asthma in children is questioned.[3,7,33,34] This is mainly based on the finding that healthy children exhibit high levels of PEF variation, with a median of 8.2%, and a 95th percentile as high as 31%.[35] These PEF variation values show large overlap with those in children with asthma,[5-7] and this limits the usefulness of PEF variation in distinguishing children with asthma from healthy children. Because these results were obtained with unreliable written PEF diaries, we decided to study PEF and FEV_1 variation in healthy schoolchildren using home spirometry *(chapter 5).* This study yielded a reliable single reference value of lung function variation for all schoolchildren, which is substantially lower that previously described in studies using mechanical PEF meters and written PEF diaries [35] (table 3).

Given the low level of lung function variation found in healthy children *(chapter 5)* and the much higher degree of lung function variation found in children with persistent asthma *(chapter 3)*, we hypothesized that home spirometry could be used as a diagnostic tool for asthma in children with nonspecific respiratory symptoms. The diagnostic study we designed to test this hypothesis, however, showed that home spirometry is of limited value in making or excluding the diagnosis of asthma in schoolchildren with nonspecific respiratory symptoms, such as cough and breathlessness, with likelihood ratios of 1.77 and 5.85 for PEF and FEV_1 variation, respectively *(chapter 6).*

Table 3. Old (1991) and new (2008) reference values for diurnal variation of PEF (and FEV_1), obtained by using mechanical PEF meters and written PEF diaries[35] and by using home spirometry with electronic data storage *(chapter 5).*

Age groups	PEF (ampl%mean)		FEV_1 (ampl%mean)	
	Mean (95%CI)	95th percentile	Mean (95%CI)	95th percentile
6-14 yr olds (n=159)*	8.2 (not available)	31.0	not available	not available
6-16 yr olds (n=204)†	6.2 (5.8-6.7)	12.3	5.7 (5.4-6.1)	11.8

*Quackeboss et al[35]; †Brouwer et al *(chapter 5);* PEF: peak expiratory flow; FEV_1: forced expiratory volume in one second; ampl%mean: Amplitude of variation % mean; CI: confidence interval.

Although the likelihood ratio of 5.85 for FEV_1 variation seems adequate, the sensitivity of increased FEV_1 variation was poor, identifying less than half of the asthmatics in the study *(chapter 6)*. Although the study was underpowered, the small difference and the complete overlap in PEF and FEV_1 variation between the asthmatics and non asthmatics limits the usefulness of home spirometry in making the diagnosis of asthma in schoolchildren with nonspecific respiratory symptoms *(chapter 6)*. Therefore, even if obtained by electronic home spirometry, both PEF and FEV_1 variation can not be used as a diagnostic tool for asthma in children with nonspecific chronic respiratory symptoms.

Overall conclusions

The studies in this thesis show that:

1 The unreliability of written PEF diaries can be overcome by using home spirometry *(chapter 2)*.

2 The poor concordance of PEF variation with other parameters of asthma severity limit the usefulness of home spirometry for monitoring disease severity in childhood asthma *(chapters 3 and 4)*.

3 The poor concordance of changes in PEF variation with changes in symptom scores in children with asthma makes it unclear which patient should respond to what change in which parameter, further limiting home spirometry as a monitoring tool in childhood asthma *(chapters 3 and 4)*.

4 The reliable single reference value of lung function variation for schoolchildren, obtained by home spirometry, is substantially lower than the one previously described *(chapter 5)*.

5 The marginal contribution of lung function variation to make the diagnosis of asthma limits home spirometry as a diagnostic tool for childhood asthma *(chapter 6)*.

6 The potential benefit of the ability of home spirometry to measure FEV_1 in addition to PEF could not be proven *(chapters 3, 4 and 6)*.

7 Based on the results presented in this thesis and the proven superiority of monitoring symptoms over lung function variation,[31] international

guidelines should discourage the use of home spirometry routinely for both monitoring and diagnosing asthma in children *(chapters 3, 4 and 6)*.

Directions for further research

1 Development of a robust classification system of poor perception and excessive symptoms to identify which patients may ultimately benefit from the use of home spirometry *(chapters 3 and 4)*.

2 Home spirometry may prove useful in monitoring other respiratory diseases displaying less variation and a more gradual change, for example in cystic fibrosis.[36] Children will have to perceive a clear benefit of their effort to prevent low adherence with long-term monitoring of home spirometry *(chapters 3, 4, 5 and 6)*.

3 In clinical studies, home spirometry in childhood asthma can provide additional information at group level (chapters 3 and 4) and although the device used will need in vivo validation within the patient group studied *(chapter 2),* the provided reference values of healthy children can be used, regardless of the device used *(chapter 5)*.

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Appendice S

English Summary

Nederlandse samenvatting

List of publications

Nawoord

Curriculum vitae

English Summary

Although the Global Initiative on Asthma (GINA) guidelines advocate home monitoring of peak flow in the follow-up of asthma to assess disease severity and to help in making the diagnosis of asthma in children, this recommendation is not based on good evidence. The evidence available to date is mainly based on written PEF diaries, which have proven to be unreliable. Because this unreliability does not apply to electronic home spirometry, home spirometers are assumed to be a suitable alternative monitoring and diagnostic tool for asthma in children. The main aim of this thesis was to assess the usefulness of home spirometry in monitoring disease severity and in making the diagnosis of childhood asthma.

Validation: All studies in this thesis used the same electronic portable spirometer (Koko Peak Pro), which had been validated *in vitro* previously.
In *chapter 2*, we examined the validity of this home spirometer *in vivo* by studying the agreement between lung function variables measured by home spirometry and those obtained by hospital lung function measurement on a pneumotachograph. The home spirometer produced reproducible and quality acceptable PEF and FEV_1 measurements. The PEF and FEV_1 measurements were significantly lower than those obtained on the hospital spirometer (mean difference in PEF (L/min): 22; 95%CI: 14–30, and mean difference in FEV_1 (L): 0.06 95%CI: 0.02–0.10). This means that, although FEV_1 and PEF measurements obtained by hospital or home spirometers can

not be used interchangeably, the home spirometer is suitable to assess diurnal variation of peak flow and FEV_1, or to longitudinally assess actual peak flow and FEV_1 at home. Therefore, the Koko Peak Pro can be used for home recording of lung function under field conditions.

Monitoring: Previous studies, using written PEF diaries, have examined the relationship between peak flow (variation) and other indices of asthma severity, and found that monitoring PEF alone is insufficient to assess asthma severity adequately. Due to the unreliability of written PEF diaries, however, it is uncertain whether these earlier results are valid.
In *chapter 3*, we used the home spirometer to assess the relationships between lung function variation, asthma symptom scores and other indices of asthma severity in children with mild-to-moderate asthma using inhaled corticosteroids. We found that the relationship of lung function variation of both PEF and FEV_1 to other parameters of asthma severity, such as airway hyperresponsiveness, bronchodilator response, asthma symptom scores, and quality of life, was highly variable between patients and, therefore, too inconsistent to be clinically useful.
In *chapter 4*, we used home spirometry to prospectively study whether symptoms, prompting the use of reliever therapy, are accompanied by changes in lung function. We found that the degree of airway narrowing at these times of respiratory symptoms is also highly variable between children with asthma. If both symptoms and lung function are monitored in asthma self-management programs, the variable concordance between the two make it unclear what change in which parameter the patient is expected to respond to, and whether this response influences clinically relevant outcomes, such as exacerbation rates and quality of life. These results limit the usefulness of home spirometry as a monitoring tool in childhood asthma.

Diagnosis: In *chapter 5*, we describe a study aimed at establishing reliable reference values for lung function variation using electronic home spirometry. We found substantially lower variation of lung function in healthy schoolchildren than previously described, with a smaller degree of overlap with values obtained in children with asthma. This prompted us to re-examine the role of home spirometry as a diagnostic tool for childhood asthma.

In *chapter 6*, we prospectively explored the usefulness of lung function variation assessed by home spirometry in diagnosing asthma in children with nonspecific respiratory symptoms, such as cough and breathlessness. Although children in whom asthma was diagnosed had a higher mean degree of PEF and FEV_1 variation than children without asthma, the overlap between the two groups was considerable, and the diagnostic value of increased PEF or FEV_1 variation in making the diagnosis of asthma in those children was limited.

Overall conclusion: The studies in this thesis showed that the unreliability of written PEF diaries can be overcome by using home spirometry. However, the relationship of PEF and FEV_1 variation to other indices of asthma severity (such as symptoms and lung function) was highly variable between patients, both cross-sectionally and longitudinally. In addition, home spirometry had poor diagnostic value in identifying asthma in children with nonspecific respiratory symptoms such as cough and breathlessness. This thesis thus shows that the usefulness of home spirometry in childhood asthma, whether for monitoring disease severity or for making the diagnosis of asthma, is limited. We propose, therefore, to remove home spirometry as a diagnostic or monitoring tool for childhood asthma from asthma guidelines.

Nederlandse samenvatting

De diagnose astma wordt bij ongeveer 4% van de kinderen in Nederland gesteld. Daarmee is het een van de meest voorkomende chronische aandoeningen bij kinderen. Astma is een aandoening van de luchtwegen, waarbij chronische ontsteking een centrale rol speelt. De luchtwegen zijn daardoor overgevoelig (hyperreactief) voor verschillende prikkels, zoals huisstofmijt, huidschilfers en haren van (huis)dieren, boom- en graspollen, en sigarettenrook. Het gevolg is dat benauwdheid optreedt door slijmvlieszwelling en het samenknijpen van de geprikkelde luchtwegen (luchtwegobstructie).

De behandeling van astma bij kinderen omvat een aantal belangrijke kernelementen.

Diagnose: Allereerst moet uiteraard de diagnose worden gesteld. De diagnose astma wordt vooral gebaseerd op de klachten die kinderen ervaren, zoals terugkerende momenten van benauwdheid, piepen en hoesten. Helaas is er geen eenduidige test om de diagnose betrouwbaar te stellen. Wel kan de verdenking op astma worden ondersteund door longfunctieonderzoek. Met dit longfunctieonderzoek kan bijvoorbeeld de éénsecondewaarde worden gemeten (de hoeveelheid lucht, in liters, die in de eerste seconde van een geforceerde uitademing wordt uitgeblazen), en de verbetering of verslechtering van deze éénsecondewaarde op respectievelijk luchtwegverwijders (reversibiliteit), of juist op prikkels (hyperreactiviteit). Het nadeel

is dat deze longfunctiemetingen in het ziekenhuis moeten plaatsvinden. Hierdoor zijn het slechts momentopnames, terwijl astma juist wordt gekenmerkt door een wisselende mate van luchtwegobstructie.

Beperking van blootstelling aan prikkels: De klachten van astma kunnen verergeren door blootstelling aan verschillende factoren zoals de eerder genoemde prikkels, maar ook als gevolg van virale luchtweginfecties en emoties. Identificatie van deze uitlokkende factoren, en waar mogelijk een verminderde blootstelling daaraan, kan het astma verbeteren en de hoeveelheid benodigde medicijnen beperken.

Medicatie: De ervaren benauwdheid kan worden bestreden door de inhalatie van luchtwegverwijders (beta-2-agonisten), die in principe aan alle kinderen met astma worden voorgeschreven. Deze luchtwegverwijders werken vaak goed en snel, maar pakken de uiteindelijke oorzaak van de benauwdheid (de chronische ontsteking) niet aan. Door de chronische ontsteking met ontstekingsremmers (inhalatie corticosteroïden), te bestrijden, worden de luchtwegen minder gevoelig en treedt de benauwdheid minder vaak op. Het ophogen of afbouwen van deze medicijnen gebeurt stapsgewijs en wordt gedaan op basis van de klachten die kinderen (nog) ervaren en de hoeveelheid luchtwegverwijders die kinderen (nog) nodig hebben.

Educatie en partnerschap: Het overdragen van kennis over astma en het aanleren van vaardigheden die nodig zijn om op de juiste manier (en op het juiste moment) inhalatiemedicijnen te gebruiken, zijn essentiële elementen van de behandeling van astma, om uiteindelijk de patiënt en zijn of haar ouders stapsgewijs meer verantwoordelijkheid te kunnen geven in het zelfmanagement van de behandeling. Het partnerschap dat de patiënt en zijn of haar ouders daarmee met de behandelaar aangaan, vormt de basis voor het vertrouwen wat nodig is om met effectief zelfmanagement het astma onder controle te krijgen en te houden.

Monitoren: Het is van belang om tijdens de behandeling regelmatig te controleren hoe het met de ziekte gaat. Niet alleen om een eventuele verslechtering van het astma snel op te sporen en te behandelen, maar ook om medicijnen af te kunnen bouwen als het goed gaat. Helaas is het zo dat veel kinderen pas heel laat aan hun

klachten merken dat het niet goed gaat met hun astma. Daarom is het, naast het bespreken van klachten en medicijngebruik, ook belangrijk om objectief te meten hoe het met het astma gaat. Daarvoor worden vooral de eerder genoemde, ziekenhuisgebonden longfunctieonderzoeken gebruikt. Hiermee wordt echter alleen de toestand op het moment van de meting bepaald. Gezien het wisselende karakter van astma zou het wellicht beter zijn om dagelijks thuis de longfunctie te bepalen. Hiervoor is indertijd de piekstroommeter ontwikkeld. Dit is een simpel apparaatje, dat de maximale snelheid van de luchtstroom (piekstroom) meet, in liters per minuut, bij een geforceerde uitademing. Hiermee zou thuis een indruk kunnen worden verkregen van de mate van vernauwing van de luchtwegen en daarmee van de variatie van het astma.

Achtergrond van dit proefschrift: Het thuis monitoren van de ernst van astma bij kinderen met behulp van piekstroom (mechanisch) of thuisspirometrie (elektronisch) wordt geadviseerd in internationale richtlijnen, zoals die van de 'Global Initiative on Asthma (GINA)'. Ook wordt toegenomen piekstroomvariatie als een diagnostisch criterium gezien. Deze stellingname is echter vooral gebaseerd op logisch redeneren; er is nauwelijks wetenschappelijk bewijs te vinden voor het nut van piekstroomregistratie bij de diagnostiek of het monitoren van astma bij kinderen. Het beperkt aanwezige bewijs is uitsluitend gebaseerd op met de hand bijgehouden piekstroomdagboekjes, die uitermate onbetrouwbaar zijn gebleken. Aangezien elektronische thuisspirometers de longfunctiewaarden op een microchip registreren en daarmee de onbetrouwbaarheid van de piekstroomdagboekjes omzeilen, wordt thuisspirometrie gezien als een nuttige methode om de ernst van astma bij kinderen te monitoren, en ook als test om de diagnose astma betrouwbaar te kunnen stellen. Het doel van dit proefschrift was om de betrouwbaarheid en het nut van thuisspirometrie te onderzoeken bij het monitoren van de ernst van astma bij kinderen, en bij het stellen of verwerpen van de diagnose astma bij kinderen.

Betrouwbaarheid van thuisspirometrie: Alle studies beschreven in dit proefschrift hebben gebruik gemaakt van een zelfde soort elektronische thuisspirometer (Koko Peak Pro). Deze thuisspirometer was al in het laboratorium *(in vitro)* gevalideerd,

door de resultaten te vergelijken met die van computersimulaties, zoals aanbevolen in de internationaal geldende richtlijnen.
In *hoofdstuk 2* onderzochten wij de betrouwbaarheid van deze thuisspirometer bij kinderen *(in vivo)*, door op hetzelfde moment de longfunctiewaarden verkregen met de thuisspirometer te vergelijken met de metingen op een longfunctieapparaat (pneumotachograaf) in het longfunctielaboratorium. De piekstroom en éénsecondewaarde verkregen met de thuisspirometer bleken goed reproduceerbaar en van acceptabele kwaliteit. Ze waren echter wel wat lager dan de waarden verkregen met de ziekenhuispneumotachograaf, waardoor metingen van thuisspirometrie niet onderling uitwisselbaar zijn met ziekenhuismetingen. De Koko Peak Pro is wel geschikt om de longfunctie thuis dagelijks te vervolgen, om daarmee de variatie van de longfunctie te berekenen.

Thuisspirometrie en het monitoren van astma: De relatie tussen piekstroomvariatie en andere uitingen van ernst van astma is eerder alleen onderzocht met behulp van de onbetrouwbaar gebleken piekstroomdagboekjes. Daarom hebben wij de variatie van longfunctie, gemeten met een thuisspirometer, vergeleken met ander maten voor de ernst van astma bij kinderen.
In *hoofdstuk 3* maakten we gebruik van elektronische thuisspirometrie om het verband (de correlatie) te bepalen tussen de variatie van longfunctie, symptoom scores en andere metingen van de ernst van het astma bij kinderen die in verband met mild tot matig persisterend astma inhalatie corticosteroïden als onderhoudsbehandeling gebruikten. Uit dit onderzoek bleek dat de correlatie tussen enerzijds de variatie van piekstroom en éénsecondewaarde en anderzijds de overige onderzochte parameters van astma (prikkelbaarheid van de luchtwegen, verandering van luchtwegobstructie na inhalatie van een luchtwegverwijder, symptoom scores en kwaliteit van leven) zeer variabel is tussen astma patiënten. Dit heeft tot gevolg dat de waarde van thuisspirometrie als instrument om de ernst van astma bij kinderen te vervolgen in de klinische praktijk beperkt is.
In *hoofdstuk 4* hebben we vervolgens onderzocht of bij een vergelijkbare groep kinderen met astma een daling in longfunctie aantoonbaar was, op het moment dat ze luchtwegverwijders wilden gaan gebruiken voor acute benauwdheidklachten. In dit onderzoek bleek dat ook de mate van daling in longfunctie ten tijde van acute

benauwdheidklachten tussen de patiënten zeer variabel was. Als kinderen met astma dagelijks thuis klachtenscores en longfunctie bijhouden is het door de variabele relatie tussen deze twee fenomenen onduidelijk of kinderen met astma hun medicatie zouden moeten aanpassen op basis van hun klachten, of op basis van een daling in longfunctie. Daarnaast is het de vraag of een dergelijke aanpassing van medicatie op geleide van het monitoren thuis, de mate van astma controle verbetert. In eerder onderzoek is geen gunstig effect aangetoond van het monitoren van piekstroom en éénsecondewaarde thuis, op belangrijke uitkomsten van astma bij kinderen. De resultaten van dit proefschrift maken nog duidelijker dat het dagelijks monitoren van piekstroom of éénsecondewaarde met thuisspirometrie geen toegevoegde waarde bij de behandeling en follow-up van kinderen met astma heeft.

Thuisspirometrie en het stellen van de diagnose astma: In *hoofdstuk 5* worden nieuwe normaalwaarden van variatie van longfunctie bij gezonde kinderen beschreven, die zijn bepaald met behulp van thuisspirometrie. De variatie van longfunctie bij gezonde kinderen bleek duidelijk lager dan eerder beschreven normaalwaarden die waren verkregen met behulp van de (onbetrouwbare) piekstroomdagboekjes, en ook minder overlap te vertonen met waarden bij kinderen met astma. Hierdoor zou thuisspirometrie wellicht een instrument kunnen zijn om de diagnose astma bij kinderen te kunnen stellen.
In *hoofdstuk 6* wordt een studie beschreven waarin we de waarde thuisspirometrie als diagnostisch instrument onderzoeken bij kinderen, bij wie de huisarts twijfelt of de klachten van hoesten of kortademigheid op astma zouden kunnen berusten. De bijdrage van thuisspirometrie aan het meer of minder waarschijnlijk maken van astma bleek echter marginaal, waardoor thuisspirometrie geen goed diagnostisch instrument is om de diagnose astma te stellen bij kinderen met aspecifieke luchtwegklachten.

Conclusies: Uit de beschreven studies in dit proefschrift blijkt dat thuisspirometrie geschikt is om in de klinische praktijk de (variatie van) longfunctie in de loop van de tijd te vervolgen, niet gehinderd door de onbetrouwbaarheid van de handgeschreven piekstroomdagboekjes. De waarde van thuisspirometrie bij

kinderen met astma blijkt echter beperkt, zowel bij het monitoren van de ernst van astma, als bij het stellen van de diagnose. Dit komt vooral omdat er zo'n groot verschil is tussen patiënten met astma in de mate van variatie van longfunctie, en de relatie daarvan met klachtenscores en andere uitingen van ernst van astma. Naar onze mening is er dus geen rol weggelegd voor thuisspirometrie bij de diagnostiek of het monitoren van astma bij kinderen, en zouden de internationale astmarichtlijnen navenant moeten worden aangepast.

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Nawoord

Zo, deze mijlpaal is bereikt en al die tijd heb ik met heel veel plezier aan de onderzoeken van dit proefschrift gewerkt. Hoewel de laatste loodjes het zwaarst wegen, heeft dit lange traject bij ons thuis ook rust gebracht. Zwolle kon als stad voor een langere tijd ons thuis zijn en mede daardoor hebben we al die leuke, lieve en interessante mensen ontmoet, die ons hebben bijgestaan in de drukte, stress, en al het 'extra naast de toch al pittige opleiding', maar ook bij de geboorte van onze twee prachtige dochters.

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Daarnaast is er een hele schare arts-assistenten kindergeneeskunde in Zwolle en Groningen en ook kinderartsen in Zwolle en Groningen die mij de ruimte hebben geboden, zowel letterlijk als figuurlijk, om dit uiteindelijk allemaal voor elkaar te krijgen. Heel erg bedankt voor jullie steun en geduld de afgelopen leuke jaren. In het bijzonder wil ik het secretariaat kindergeneeskunde in Zwolle bedanken, met aan het hoofd Marion Overmars, voor de professionele hulp die jullie hebben geboden en interesse die jullie altijd hebben getoond.

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Curriculum Vitae

Alwin Foppe Jan Brouwer werd geboren op 8 april 1975 in Groningen en is opgegroeid in Sexbierum (FRL). Na het behalen van zijn atheneum diploma aan de Rijksscholengemeenschap 'Simon Vestdijk' in Harlingen in 1993, startte hij met de studie Geneeskunde aan de Rijksuniversiteit Groningen. In 1998 behaalde hij zijn doctoraal examen en in 2000 zijn artsexamen (cum laude). Van oktober 2000 tot de start van de opleiding tot kinderarts werkte hij als arts-assistent kindergeneeskunde in het ziekenhuis 'de Weezenlanden' in Zwolle, alwaar de basis is gelegd voor de onderzoeken beschreven in dit proefschrift. Op 1 april 2002 startte hij in een combinatietraject van opleiding en onderzoek (AGIKO-schap) aan het Beatrix Kinderziekenhuis van het Universitair Medisch Centrum Groningen, met als affiliatie de 'Amalia Kinderafdeling' van de Isala klinieken in Zwolle. Al het onderzoek beschreven in dit proefschrift, is uitgedacht en uitgevoerd aan de 'Amalia Kinderafdeling' van de Isala klinieken in Zwolle. Na afronding van dit proefschrift is hij begonnen aan het laatste half jaar van de opleiding tot kinderarts in het Beatrix Kinderziekenhuis van het Universitair Medisch Centrum Groningen. In 2003 is hij getrouwd met Teatske Leenstra, samen hebben zij twee schatten van dochters: Famke Anne (2007) en Nynke Mirthe (2009).

Dit proefschrift is gedrukt op papier dat afkomstig is uit duurzaam beheerde bossen.